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ASIAN INFLUENZA IN THE UNITED STATES*

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THE worldwide pandemic of Asian strain influenza during 1957 was the most dramatic epidemiologic phenomenon since the pandemics of influenza in 1918 and in 1889–1890. The accuracy of the predictions, the duration of the advanced warnings and the scope of the effort to control it in this country are unique in the history of organized medicine and public health.

In this presentation, I would like (1) to discuss briefly the remarkable character of the predictions that were made; (2) to describe the course of the epidemic in this country, including the wave of mortality in the winter and spring of this year, and (3) finally, to make a few remarks about what we can anticipate in the future.

THE PREDICTIONS

From the moment last spring when Dr. Maurice Hilleman announced that six strains of influenza virus from the Hong Kong epidemic were antigenically distinct from previously known strains, essentially all epidemiologists throughout the world agreed to the prediction that epidemic influenza would spread inexorably on a global scale.

The basis for this prediction was not any unusual epidemiologic or clinical aspect of the Hong Kong epidemic. On the contrary, this and the other epidemics in the Far East, in Manila, Formosa and Singapore seemed entirely characteristic of the waves of influenza that come every few years. More important was the fact that the concept of major antigenic shifts in influenza viruses had been developing for many years, and Dr. Hilleman's

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laboratory findings provided the factual evidence in support of a theoretic doctrine that had been long anticipated. Our chairman today has been a leading contributor to this doctrine.

It was unanimously agreed that epidemic influenza would spread through the Southern Hemisphere during the then winter months, but that it probably would not spread through the Northern Hemisphere until the coming fall or winter. Introduction and multiple seeding of the virus could be anticipated at once, since there is such a large and continuing international travel. Subsequent events abundantly substantiated these predictions.

There was no agreement among the experts regarding the possible severity of the epidemic. Some feared further mutations, leading to virulence of the order of the 1918 epidemic. Others predicted a second wave, with virulent secondary bacterial invaders. Still others felt that the mild character of the epidemics in Hong Kong and Singapore would probably set the pattern for the worldwide picture, and believed that the concept of a second-wave was not supported by the experience with influenza of the last 30 years.

Fortunately, the severity and virulence of the Asian influenza epidemic were not high. The epidemic as measured by excess influenza pneumonia mortality was only slightly more severe than the influenza A prime epidemic of 1953, and it was considerably less severe than the influenza A epidemic of 1943. Secondary bacterial invaders caused some cases of pneumonia, but nothing comparable to 1918.

A second wave of mortality did occur. This will be described later. Suffice it here to say it was different from all predictions. Thus, some of the predictions that were immediately made and unanimously agreed to in the spring of 1957 were remarkably consistent and amazingly true. Others were remarkably variable to an equal degree.

The Epidemic

Almost at once following Dr. Hilleman's announcement, evidence of the introduction of the influenza virus to this country became apparent (figure 1). The first outbreak occurred on the East Coast, on a Navy destroyer at Newport Naval Base in Rhode Island. Shortly thereafter epidemics were identified at the Naval Training Center in San Diego, among Army recruits at Fort Ord, and on numerous ships coming to the Pacific shore from the Far East.

The first civilian epidemic occurred among high school girls at a convention in late June at Davis, California. Then in the last days of June a sharp outbreak occurred at a religious conference at Grinnell, Iowa, attended by 1,688 participants from 43 states and nine foreign countries.

A chartered railroad coach carried 100 delegates from California to Grinnell. One member of the delegation had been present at the conference in Davis. She developed a respiratory illness en route. On arrival the

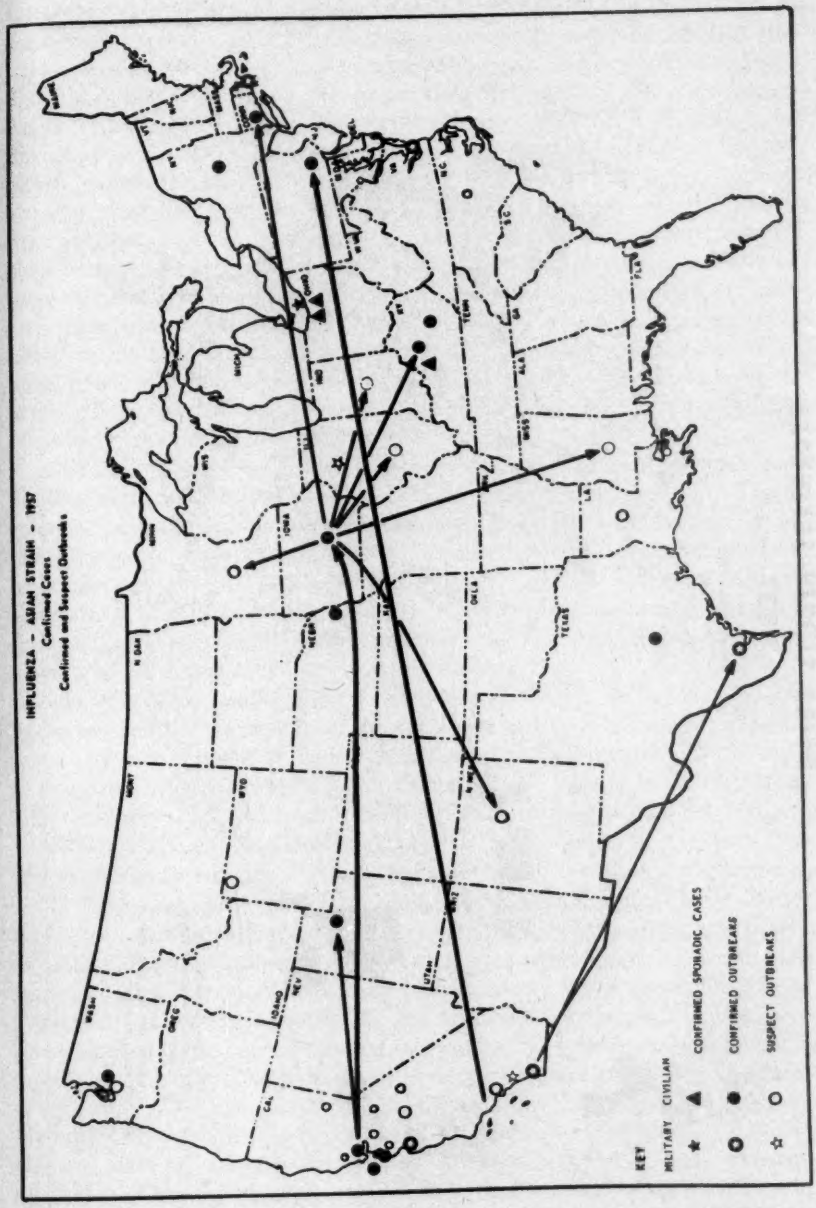
INFLUENZA - ASIAN STRAIN - 1957
Confirmed Cases
Confirmed and Suspect Outbreaks
KEY
MILITARY CIVILIAN
CONFIRMED SPORADIC CASES
CONFIRMED OUTBREAKS
SUSPECT OUTBREAKS

FIG. 1.

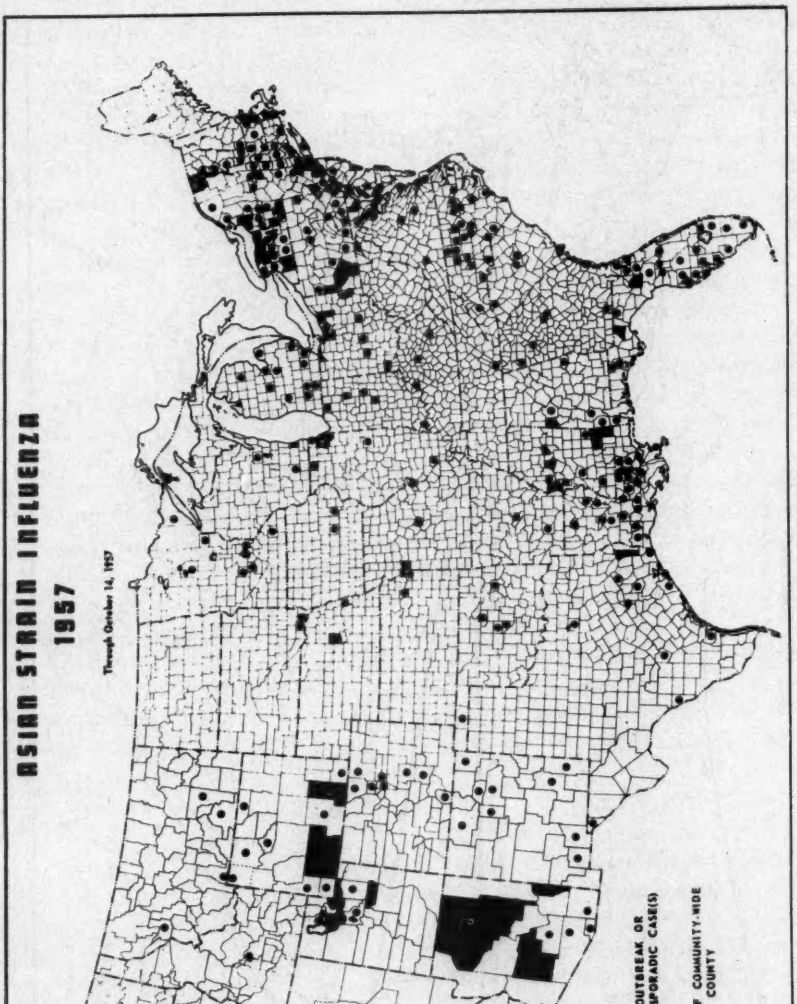
ASIAN STRAIN INFLUENZA
1957
Through October 14, 1957
KEY:
LOCALIZED OUTBREAK OR CONFIRMED SPORADIC CASE(S) IN COUNTY
EVIDENCE OF COMMUNITY-WIDE EPIDEMIC IN COUNTY
(County Entirely Black)

FIG. 2.

California delegation was distributed widely to each of the dormitories on the college grounds. There was intense crowding, since the 1,688 participants were housed in facilities normally designed for only 900 students.

The epidemic disrupted the conference, and on July 1 the delegations began returning to their home states. Many of these were traced and identified as having Asian strain influenza, so that widespread seeding was clearly demonstrated.

The remarkable finding during the summer months was the lack of dynamic spread of the infection in the country. Although many introductions were identified, many, many more must have occurred. Outbreaks were consistently limited to the classic epidemiologic circumstances where large numbers of people were unusually crowded together in buses, trains, dormitories or barracks. Repeated studies of cases introduced into homes often failed to demonstrate frequent infection, even of close household contacts. Thus, there were clear limitations to the infectiousness of this newly identified virus during the summer months.

The first dynamic spread of Asian strain influenza throughout a community occurred in Tangipahoa Parish, Louisiana. Here, in August, epidemics developed among school children and industries and spread widely throughout the community. It was significant, and a harbinger of events to come, that in this parish schools opened early in August because of agricultural need for children to assist in gathering the strawberry crop in the spring. Similar limited, community-wide spread occurred in the cotton-picking belt of Mayflower County, Mississippi.

These observations warned us that schools might be a crucial factor in the initiation of community-wide epidemics, and such turned out to be the case. By mid-September reports of increased absenteeism in schools began to flow from widely scattered parts of the country. Early in October many hundreds of schools had closed for sheer want of both pupils and teachers.

Figure 2 shows the status of reports to the Influenza Surveillance Unit up to October 14. Figure 3 shows the extent of reports through December 2.

In recording the influenza epidemic, the Communicable Disease Center, through its Influenza Surveillance Unit, had the closest collaboration with all state and territorial health departments, with over 100 virus laboratories, with the Armed Services, and many other components of the Public Health Service. The National Health Survey, established primarily for other purposes, was able to organize a regular collecting system on a nationwide sample basis, and produced most valuable current measures of the frequency of minor disabling and febrile disease. Thanks to Dr. L. Holland Whitney, Medical Director of the American Telephone and Telegraph Company, absentee data on selected workers in 38 cities were also made currently available. Thus, a large volume of statistical material permitted the description of the epidemic on an unprecedented scale.

The measures of this epidemic are illustrated in figure 4. The similarity

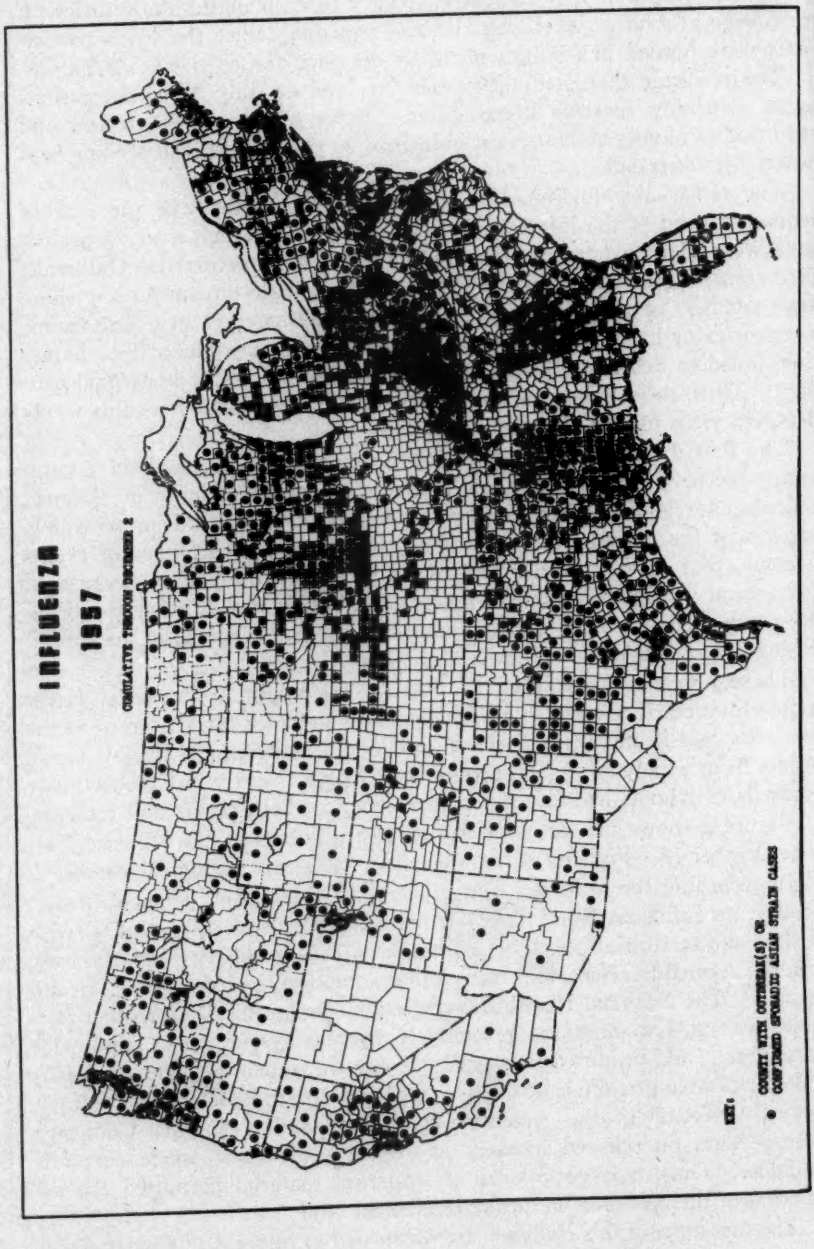
INFLUENZA
1957
CUMULATIVE THROUGH DECEMBER 8
KEY:
COUNTY WITH OUTBREAK(S) OR
CONFIRMED SPORADIC ASIAN STRAIN CASES

FIG. 3.

and concurrence of these reports are remarkable. The narrative reports from the epidemiologists regarding the occurrence of definite outbreaks by counties, the prevalence of influenza-like diseases as revealed in the National Health Survey, and the excess in industrial absenteeism all rise and fall essentially in parallel. The peak of the epidemic, for the nation as a whole, was clearly in the third week in October, with a steady and rapid decline thereafter. The epidemic was essentially over by Thanksgiving.

The old and classic index of epidemic influenza is an excess of influenza-pneumonia mortality. This also is shown on figure 4, but the excess rises later, reaches a peak two to three weeks later, and then subsides. This delay

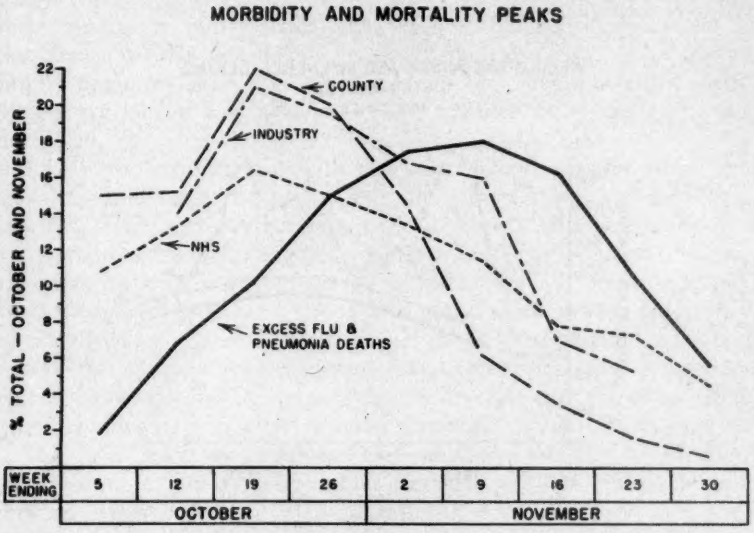

FIG. 4.

in mortality reflects the duration of disease in the patient, the later time of infection of older and debilitated persons, and some delay in reporting.

You are all familiar with the comprehensive national program for the anticipated epidemic that was organized under the leadership of the Surgeon General of the Public Health Service during the early summer months, well before the first community-wide epidemics developed. Organized medicine, all official health agencies, the hospital administrators of the country, and all who would have administrative responsibilities in the epidemic situation, were coördinated in a common plan and kept informed of the progress of the epidemic.

The pharmaceutic firms of the nation undertook a crash program of vaccine production. Before the end of the epidemic a veritable Niagara of vaccine was flowing to fill the apparently insatiable but short-lived popular

demand for immunization. Had the epidemic held off only a few weeks longer, tens of millions more citizens would have been immunized. As it was, over 40,000,000 doses of vaccine were made available, and evidence that it was at least partially effective is now being reported from many carefully controlled studies.

By December the epidemic appeared to have subsided throughout the nation, only to be followed early in the New Year by a sharp increase in mortality, due to influenza-pneumonia and all other causes. This so-called "second wave" has approximated the October-November epidemic in severity (figure 5). In some cities the increased mortality in January, February and March exceeded that in October and November. In many cities it continued over a longer period of time.

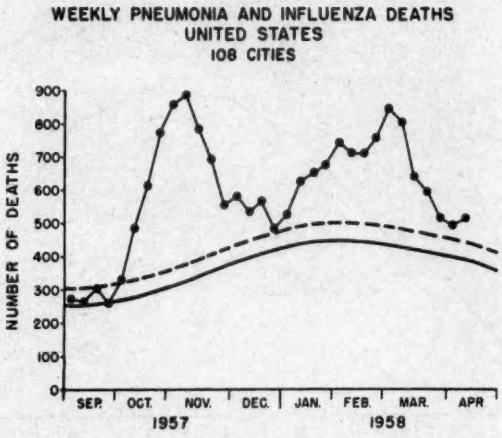

FIG. 5.

No explanation for this marked excess mortality has been found. There is no comparable event on record in the past 50 years. Normally excess mortality is associated with clear-cut influenza epidemics. Such could not be found, on a community-wide basis, during the winter and spring. The National Health Survey revealed a normal winter expectancy of febrile minor illness. Schools were not closing. Industrial absenteeism was not high.

A study of the age of the excess deaths revealed that they predominated in the older age groups—65 years of age and over. Otherwise, there were few characteristic features. A small number of isolations of Asian strain influenza has been reported from some cities from lungs of fatal cases during this period. Localized epidemics of influenza in small and crowded populations on certain hospital wards in schools and military groups have occurred in low frequency. Some of the outbreaks have been associated

with severe and even fatal staphylococcal pneumonia. At the present time, however, the evidence does not seem sufficient to account for this major wave of mortality, either on the basis of unrecognized influenza spreading silently among older persons, or of the prevalence of particularly virulent strains of staphylococcus in the community at large. The causes for this "second wave" of mortality without apparent influenza remain enigmatic.

The Future

What of the future? It is apparent that a major antigenic shift in Type A influenza virus has occurred and has led to a global epidemic in a pattern which has long been anticipated. The most commonly anticipated prediction for the future is that this Asian strain will dominate the influenza picture for the next decade or longer, with epidemics every few years, until the immunity of the total population reaches a level where this particular antigen no longer can survive. Then another antigenic shift can be anticipated.

I have no basic quarrel with this concept, but for discussion at this panel I question that the situation is this simple. We are due for some surprises. The 1957 Asian outbreak has unique characteristics distinct from several of the other antigenic shifts which have occurred. Certainly, it is markedly different from the 1947 event, when A prime influenza replaced the preceding Type A virus. No global epidemic was apparent then. No tracing of the chain of events around the world was recorded. In fact, in 1947 the A prime epidemic wave was exceedingly mild and seemed to involve limited geographic areas. It took several years for us to recognize how promptly and completely A prime virus had replaced the A type strain.

The 1957 Asian event has striking similarities to the 1918 pandemic, and even more similarities to the pandemic of 1889–90. These were dramatic events seeming to have origins in a definite focus and then to spread on a global scale.

Thus, I would like to suggest that Asian influenza of 1957 may be a unique phenomenon like the 1918 and 1889 pandemics and distinct from the interpandemic influenza outbreaks which occur every few years. This construction of ideas suggests that Asian strain influenza may have a relatively short life of activity and then disappear. At least this is good material for discussion at this symposium, and one thing to me is rather certain—we can anticipate continuing surprises in the field of influenza before we learn enough to predict future events with precision and eventually learn how to control or even eradicate the disease.

Summario in Interlingua

Post le annuncio, le primavera passate, del isolation de sex antigenicamente distincte racias de virus de influenza ab le epidemia de Hong Kong, expertos in omne partes del mundo prediceva un epidemia global. Le frappante accuratia de iste pre-

diction e le character remarcabile de altere predictiones facite con respecto a ille epidemia es discutite.

Le prime eruption del morbo in le Statos Unite occurreva al bordo de un nave del marina, anchorate in un porto de Rhode Island. Subsequentemente, eruptiones del morbo esseva reportate inter altere gruppos de personal militar e inter dense populationes civil. Tamen, il esseva solmente post le comenciamento del anno scholari que epidemias afficiente integre communitates comenciava occurrer.

Le epidemia attingeva su culmine in octobre. In decembre illo apparentemente habeva subsidite. Iste declino esseva sequite per un si-appellate "secunde unda" de mortalitate durante le prime menses del anno currente.

Que va esser le futuro de influenza asian? Le majoritate del expertos predice varie grados de predominantia del morbo durante le periodo de tempore que es requirite usque le population total attinge un nivello de immunitate a que le antigeno perde omne possibilitate de superviver. Tamen, considerante le dissimilaritates inter iste epidemia e le epidemias que recurre in cyclos de alicun annos (specialmente le unda de influenza A-un de 1947) e, in plus, considerante le similaritates inter le eruption de 1957 e le pandemias de 1918 e 1889–90, iste autor suggere le possibilitate del disparition de influenza asian ab le scena post un relativemente breve periodo de activitate.

THE CLINICAL EPIDEMIOLOGY OF ASIAN INFLUENZA *

By Fred M. Davenport, M.D., and Albert V. Hennessy, M.D.,
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In February, 1957, viruses belonging to a previously unrecognized family of influenza A strains emerged from North China and within four months were disseminated throughout the globe.[1, 2] The seeding of the world's population by what is now called Asian influenza was followed at various intervals by sharp outbreaks associated with a high attack rate.

A major antigenic rearrangement, resulting in the appearance of another family of strains, is not a new phenomenon. With the passage of time, four successive shifts have occurred, followed, respectively, by the four successive periods of prevalence of swinelike, A, A-prime, and now Asian strains. The degree of rearrangement that took place among the antigens when each family became prevalent was apparently of about the same order of magnitude. Throughout the first three periods the clinical and epidemiologic characteristics of influenza remained quite uniform, with one notable exception. The swine epoch, which extended for 10 to 15 years, was marked by the pandemic of 1918–19, a visitation associated with an unusually virulent strain of virus.

Throughout the same three periods the incidence of influenza A as judged by excess mortality declined progressively, despite the occurrence of these three major antigenic shifts.[3] Clearly, then, knowledge of antigenic structure does not permit an accurate prediction of the incidence and virulence that may be encountered when a new family of viruses appears.

By early June, 1957, Asian influenza had spread with alarming speed, and there were disturbing newspaper accounts of an unusual number of influenza-associated deaths. Those events caused great concern and raised the spectre of 1918–19. The consequences of an Asian influenza epidemic occurring in the wintertime could not be forecast and were feared.

Although from the limited information available it seemed unlikely that the 1918–19 catastrophe was about to be repeated, nevertheless it was realized that current knowledge did not justify assuming an attitude that would disregard that possibility. Obviously, accurate information was critically

* From the Symposium on Influenza, presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, April 28, 1958.

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Certain of these studies were conducted under the auspices of the Commission on Influenza, Armed Forces Epidemiological Board, Office of the Surgeon General, United States Army, Washington, D. C.

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needed. For this purpose, a reconnaissance was made early in June to Australia, the Philippines, Japan and Hawaii; and in August, in coöperation with Chilean investigators, a study was established in Santiago. Both efforts were carried out under the auspices of the Armed Forces Epidemiological Board. The data derived support the thesis that, antigenically speaking, Asian influenza is not a completely "newe acquayantance." [4] They demonstrate that the emergence of these strains has not changed the basic clinical or epidemiologic characteristics of influenza A.

A primary concern of these field investigations was to gauge the virulence of Asian influenza virus. The principal criterion used was whether deaths from Asian influenza and pneumonia were occurring chiefly at the extremes

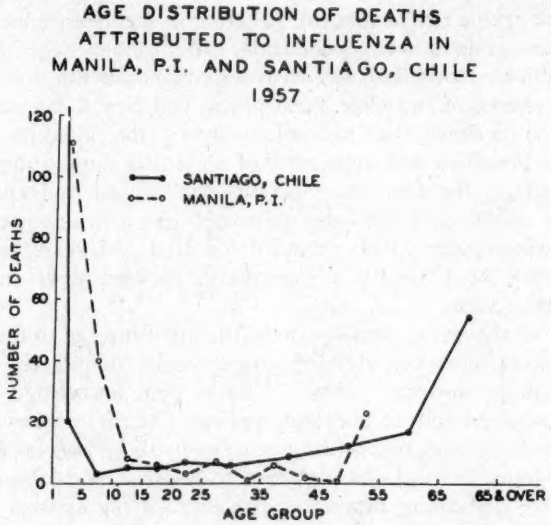

FIG. 1.

of life, thereby producing the familiar skewed, U-shaped mortality curve, or whether, as in 1918–19, deaths were also prominent in the 20- to 40-year age group, resulting in a W-shaped mortality curve. The first important information came from Dr. A. Alomia,[5] Manila Health Department, who had determined the age distribution of 208 deaths attributed to influenza as of mid-June (figure 1). The number of deaths reported is plotted by five-year age intervals until the age of 50. Thereafter the recorded deaths were placed in a single category and are plotted opposite the 55-year point on the scale. There is nothing in these data to suggest a W-shaped mortality curve. Later, an age distribution was obtained for 1,430 deaths in Santiago, Chile, attributed to influenza, pneumonia and bronchopneumonia during their epidemic of July and August, 1957.[6] Here again there was no

prominence of influenza-associated deaths in the middle years of life. These crude data and the more exact age-specific mortality rates which became available subsequently demonstrated that Asian strains were not unusually virulent.

The clinical manifestations of uncomplicated Asian influenza in the Orient and in South America were found to be the common ones. In Chile it was possible to obtain quite accurate information about the relationship of Asian influenza to the pneumonias and deaths that supervened. The results of these important studies have been published [6, 7, 8] and will not be reviewed here in detail. Suffice it to say that following the highest attack rate of influenza experienced in Chile since 1918–19, the number of deaths from grippe, pneumonia and bronchopneumonia increased 5.1 times over that found in the same period of the previous year. While a larger number of patients with pneumonia was encountered, the case fatality and the age distribution of fatal cases were the same as those observed in the last five years. There were no strikingly unusual clinical features of the pneumonias. In general they were related to the common bacterial pathogens and responded well to customary antimicrobial therapy. Fatal cases occurred in three circumstances: (1) overwhelming infection with organisms sensitive to antibiotics occurring in persons whose ultimate survival was already jeopardized by neglect, chronic illness, debility or pregnancy; (2) infection with staphylococci resistant to antimicrobial therapy (from the lungs of approximately 50% of the fatal cases studied, staphylococci were cultured); (3) in a few cases death was associated with a hemorrhagic pneumonia, at times showing hyaline membrane formation. No significant organism was cultured from these cases.

At this stage of the analysis the emergence of a new family of strains had produced no unfamiliar consequences. Another way of testing whether the Asian strains were distorting the customary clinical or epidemiologic pattern of influenza A was to determine the attack rate by age. If Asian influenza was an antigenic "newe acquayantance," then one would expect the attack rates to be uniform at all ages, since the population would in that case have no antibody defenses against infection. Data obtained from Santiago and elsewhere indicated that the population was obviously not defenseless. A retrospective house-to-house survey was carried out in Santiago by Chilean investigators on September 13 and 14. They canvassed 2,862 families containing 15,339 persons who lived in 50 blocks of houses selected so as to constitute a 1% stratified random sample of the whole population.[6] The attack rate (figure 2) was highest in childhood and declined thereafter progressively with age, a finding remarkably consistent with the classic data of Collins [9] on the age distribution of influenza in 1918, 1929 and 1943. How can one explain this phenomenon? The most logical explanation yet offered for the relative immunity of the older segments of the population in all epidemics is the acquisition, with age and

repeated infection, of a composite of antibodies directed against most of the antigens that comprise strains of influenza A, even though the presence of strain-specific antibody may not be demonstrable. This explanation was derived from studies carried out in 1952 which correlated the distribution by age of antibodies against A-prime, A and swine strains and the classic descriptions of age incidence of influenza A (figure 3). The data were obtained while influenza A-prime was of paramount importance. The antibody spectrum in the first decade of life was the narrowest and the attack rate the highest. At that time children possessed antibody only against A-prime strains. In the next two decades when the antibody spectrum broadened to encompass A as well as A-prime viruses, the attack rate declined. In persons 30 or more years of age, some antibody against all three families of A strains could be demonstrated, and although antibody levels

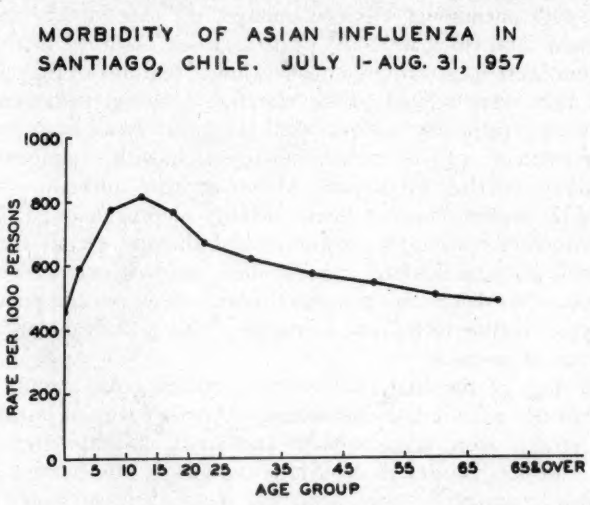

FIG. 2.

to A-prime isolates were the lowest, the resistance of persons in this age category increased progressively.

Obviously, now as then, the marked reduction in incidence of the older age groups does not appear to correlate strictly with the presence of strain-specific antibody. Clearly, the elements of composite antibody which are not strain-specific play a major protective role. However, as Mulder first pointed out, in the case of Asian influenza there is, in addition, a strain-specific component which may be operative in the closing decades of life. Mulder found high levels of antibody in a small proportion of sera collected in Holland before their summer epidemic of 1957 from persons 70 or more years of age. He inferred that an Asian-like strain had been prevalent many years ago, possibly during the pandemic of 1889–90.[10] Fundamentally,

Mulder's hypothesis represents another application of "the doctrine of original antigenic sin," [11] which states that the major antigens of the strains of primary infection in childhood orient the antibody-forming mechanism so that throughout life the primary antibody is reinforced by all subsequent exposures to antigenically related strains.

Because the epidemiologic implications of Mulder's hypothesis are so important, extensive studies were carried out in Ann Arbor to examine his basis for it. Sera were collected by age from the wards of the University of Michigan Hospital during the preëpidemic period of June and July, 1957. The geometric mean levels of hemagglutination-inhibiting antibody were determined for two-year age intervals in these specimens, and the results

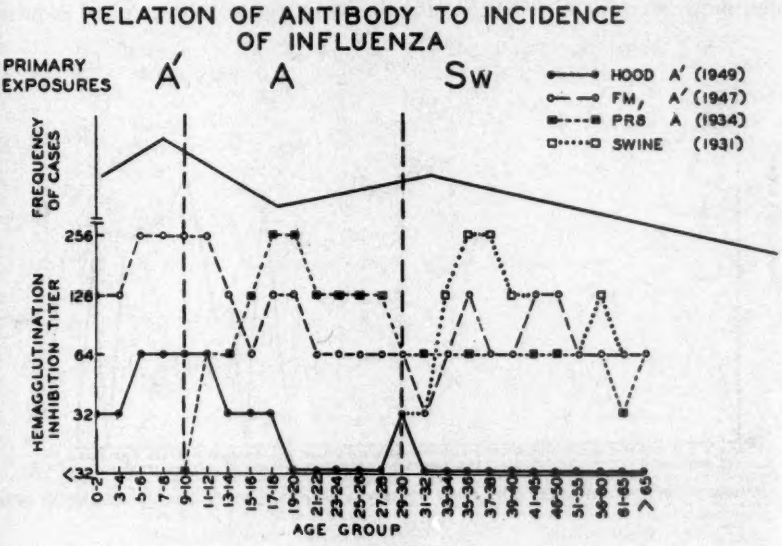

FIG. 3.

are shown in figure 4. Usually 25 samples were tested at each interval. In our experience, persons less than 60 years of age characteristically did not exhibit antibody, whereas persons 65 or more years old generally did. The high levels of Asian antibody found in sera of persons 65 or more years of age indicate that this cohort had encountered the major antigens of Asian virus in a previous infection during a former period of widespread prevalence. It may be calculated that that period of prevalence encompassed the pandemic of 1889–90, and perhaps extended from 1889 to 1897.

Another line of evidence which supports the conclusion that the major antigens of Asian viruses were prevalent many years ago is that persons 80 or more years of age showed a conspicuously greater antibody response to

a standard dose of Asian virus vaccine than did persons in younger age groups.[12]

These data support Mulder's hypothesis and indicate that some of the major antigens characteristic of strains remotely prevalent may be recycled after many years in strains that emerge again. This view is compatible with the thesis that the number of antigens of influenza A is finite, and that recycling is inevitable if influenza viruses are to survive.[13, 14] The phenomenon of recycling holds promise for capturing all of the essential antigens of influenza viruses, and when this is accomplished an influenza virus vaccine that will be maximally effective at all times may be compounded.

What, then, may the mechanism of antigenic recycling be? I would like to suggest one mechanism the validity of which can be tested. It has been shown that the distribution of antibody by age to swine, A and A-prime

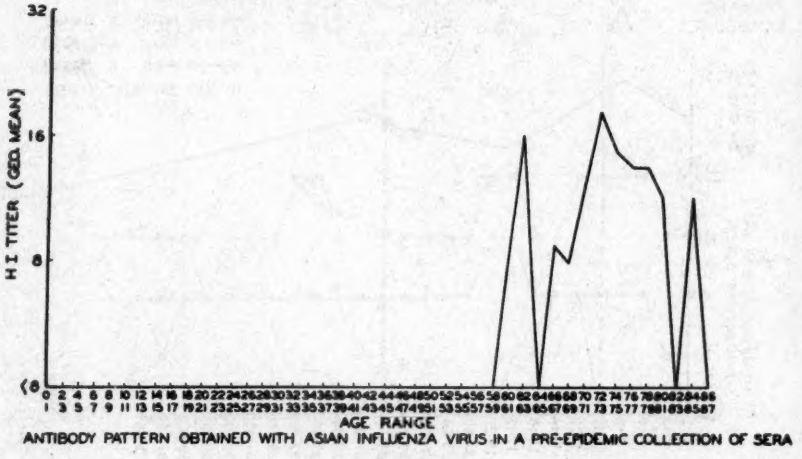

FIG. 4.

strains is essentially the same in the United States, England [15] and Czechoslovakia.[16] Dr. Mulder has described antibody patterns to swine and Asian strains in sera collected from Holland that are like those found in sera from Ann Arbor.[10] Through the coöperation of the 406th Medical General Laboratory, Camp Zama, Japan, we were furnished a collection of sera pooled by age obtained from Japanese citizens after their epidemic of Asian influenza of June. Pools of identical size and age distribution were made from sera collected in Ann Arbor in the preëpidemic period. The results of HI testing with swine, PR8, FM1 and A/AA/23/57 in both sets of sera are shown in figure 5. It is apparent that A-prime, A and swine antibodies are found in both populations at approximately the same ages and levels.

Asian antibody is found after age 60 in both populations, but in childhood, adolescence and young adult life Asian antibody is found only in the

sera from Japan, reflecting the known high attack rates that occurred at these ages during the epidemic of 1957.

The similarity in antibody content of the human race resident in different parts of the world is indicated by these data and, in theory, this circumstance provides an antibody basis for the selection of mutants whereby antigens previously dominant may become resurgent. If we assume that antibody against strains of the 1889–97 period were built up in the population by recurrent exposures, antigens of the Asian character would become relatively ineffectual for spreading. Hence, a major antigenic rearrangement in which other components become dominant might be required for survival.

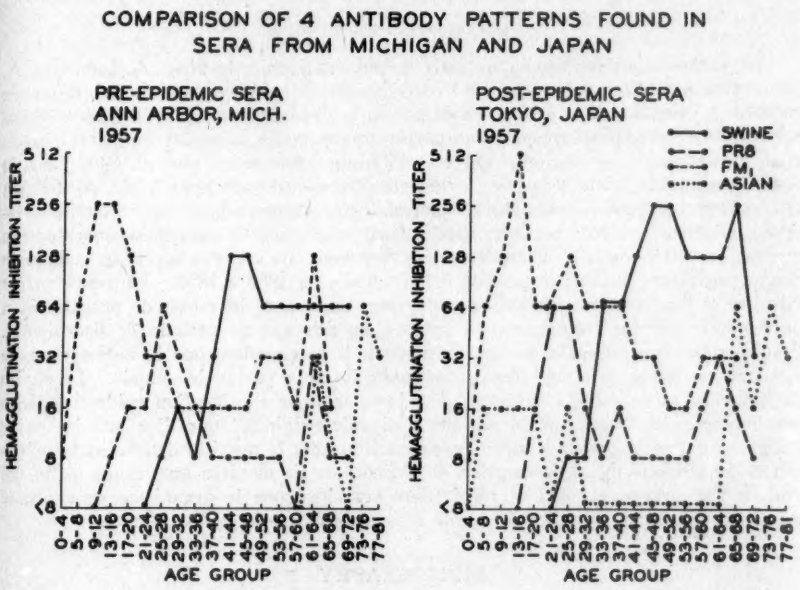

FIG. 5.

Thereafter the process of saturation of the population with antibody would begin again. With the passage of time the antibody gap for Asian strains is widened to 65 or more years of age—the back door has opened so that Asian antigen can again provide a feature that favors spreading within that vulnerable group. This hypothesis has the merit of being testable by observing the influence of the accumulation of Asian antibody in the population upon such antigenic changes as may occur subsequently.

SUMMARY

Asian influenza is not a new experience as judged by clinical, epidemiologic, immunologic or serologic criteria. Immunity from Asian influenza, as with other strains, seems to relate principally to composite antibody built

up through multiple exposures to the many antigenic variants of influenza A. In persons over 65 years of age the specific component contributed by antibody sustained from earlier experiences with Asian antigen plays a subordinate though serologically discernible role. The emergence of Asian strains has been a valuable experience through which the resurgence of antigens has been demonstrated for the first time. It has added clear support for interpretations made from earlier observations on age distribution of antibodies and their relation to initial exposure and immunity. Finally, I would like to state that pursuit of the clinical epidemiology of Asian influenza has been an exciting and rewarding experience.

SUMMARIO IN INTERLINGUA

Le racias asian representa un nove familia antigenic de virus de influenza A. Lor diffusion ab China septentrional in februario 1957 sublevava un numero de grave questiones. Studios in le campo, effectuate in le Oriente e in Chile in Sud-America per medios clinic, epidemiologic, e serologic, ha producite certe importante responsas a ille questiones. Le resultatos del investigationes demonstra que, ab le puncto de vista antigenic, le racias asian non es un completemente nove experientia. Influenza asian obediva al basic normas clinic, epidemiologic, e immunologic que es characteristic de influenza A. Non occurreva un inusual expression de virulentia, como esseva le caso in 1918 e 1919. Considerationes serologic indica que un virus asianoide esseva prevalente durante le periodo del pandemia de 1889 e 1890. Isto es le prime vice que il pote esser monstrate que antigenos dominante in racias de prevalentia a un tempore anterior recomencia lor cyclo a un subsequente periodo de prevalentia. Como explication possibile de iste phenomeno il es signalate que le anticorpore de humanos contra le virus de influenza es simile in omne partes del mundo. Le studio de influenza asian servi a sublinear additionalmente le signification epidemiologic e immunologic del "doctrina del peccato antigenic original," que dice que le major antigenos del pathogenos de infection primari durante le pueritia determina le orientation del mechanismo de generation de anticorpore de maniera que, usque al fin del vita, le anticorpore primari es reinfortiate quandocunque le organismo es exponite a un pathogeno que es antigenicamente affin a un del pathogenos primari.

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A STUDY OF THE EFFECTS OF TYPE A (ASIAN STRAIN) INFLUENZA ON THE CARDIOVASCULAR SYSTEM OF MAN*†

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THE foreknowledge of the approaching pandemic of Asian influenza permitted for the first time the planning of programs for the study of many aspects of the disease in different areas of the country. The present report concerns observations on the influence of Asian influenza on the cardiovascular system of man.

Initially it was planned to study fairly intensively patients with acute uncomplicated influenza. Unfortunately, however, the disease reached the New Orleans area in epidemic proportions in July and August, 1957, even before it involved other sections of the country, except for occasional small outbreaks among soldiers, sailors and travelers returning to the United States. This early epidemic precluded the use of all available facilities and the desired selectivity of patients initially, so that only certain aspects of the disease could be studied. Furthermore, careful clinical examination had to be performed, since virologic diagnosis could not be established until the patient had recovered from the disease.

MATERIALS AND METHODS

Thirty-four patients, ranging in age from 12 to 70 (mean, 29) years, were included in this series of whom all but four were under 40 years of age. The distribution by age, sex (12 men and 22 women) and color (nine white and 25 Negro) was to be expected from the nature of the study and the patient population of Charity Hospital. Although the diagnosis of Asian influenza during the height of the epidemic was readily established on the basis of clinical data alone, laboratory confirmation was also obtained in 30 of the 34 patients. Throughout hospitalization, all patients were observed at four-hour intervals, when temperature, pulse and respiratory rates, and systolic and diastolic blood pressures were recorded.

The patients were selected on the following bases and divided into two groups for convenience of presentation:

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Group 1 consisted of 30 patients:

1. Twenty with the typical clinical picture of early influenza on admission to the outpatient department of the Hospital had all or most of the investigative procedures mentioned performed on them.
2. Ten patients had been hospitalized because of the severity of their pulmonary infection or because they did not have adequate home care. Routine electrocardiographic studies revealed abnormalities in all, and virologic confirmation of the diagnosis was established in all.

Group 2 consisted of four patients who experienced severe cardiovascular complications of influenza. These will be discussed in a separate section of this report.

In addition to routine clinical and laboratory examinations, the following studies were obtained when practicable: fluid and electrolyte measurements, adrenal cortical function, serial standard electrocardiograms, spatial vectorcardiograms, digital rheoplethysmograms, renal and hepatic function, bronchoscopic biopsies and cytologic examinations. The magnitude of the clinical problems is apparent when it is realized that the first outpatients with influenza seen at the Charity Hospital during the early days of August, 1957, increased within four weeks from a few dozen to well over 1,000 a day. The epidemic reached its peak about the first week of September, 1957, and within a week or 10 days patients suitable for study were no longer available. Overtaxed hospital facilities, and illness among the professional and technical personnel interfered with the studies.

Group 1

Patients with Typical Influenza Uncomplicated by Clinically Evident Cardiovascular Disturbances

Clinical Features

Contact: Nine of the 30 patients with typical manifestations had a history of known contact with influenza within the few days preceding illness. All, however, were from the New Orleans area, where thousands of people were ill with the disease.

Prodrome: Only two patients stated that they had had any preceding illness. Both had had a mild upper respiratory infection one week before the onset of the influenza. This did not appear to alter the course of the later infection.

Onset: All but three patients noted an acute onset of symptoms, although not of maximal intensity initially. These usually consisted of fever, headache, chilly sensations or myalgia, in varying combinations. Within a matter of hours the clinical picture had become complete. Two patients noted a progressive onset of symptoms over a period of approximately 18

to 24 hours, and one patient observed a gradual increase in existent respiratory symptoms over a period of a day and a half.

Symptoms: Almost all patients suffered from fever, chills or, usually, chilly sensations, cough, headache and myalgia. Approximately one third complained of conjunctival burning or discomfort and lacrimation. A similar proportion complained of pain in the chest, which was described as retrosternal soreness, aching or tightness. A single patient with complicating pneumonia had typical pleuritic pain. Nine patients had sore throat, which was described as a scratchy or dry feeling. Five had mild nausea and vomiting early in the course of their illness. Hemoptysis of the streaking type was noted in two patients with pneumonia and in two with uncomplicated influenza. Dyspnea was experienced by only four patients, two of whom had pneumonia, one with uncomplicated influenza and one with bronchial asthma. Spontaneous epistaxis and vague abdominal pain each occurred in a single patient. In only one patient was there at any time during observation a complaint that could be referred to the cardiovascular system. This patient will be considered more fully later under the section entitled "Blood Pressure Changes."

Physical Findings: There was a paucity of such abnormalities. Flushing was observed in two patients, both Caucasians. The most common physical finding was moderate injection of the nasopharynx. Typical streptococcal pharyngitis in one patient was confirmed by bacteriologic studies. Fifteen patients had conjunctival injection. Only two had enlarged cervical lymph nodes. Whereas transitory rhonchi and wheezes were noted in four patients with uncomplicated influenza, in only three with pneumonia were fine râles noted. Cyanosis and bronchial breathing were observed in one patient each. In six additional patients with uncomplicated influenza the altered breath sounds were patently abnormal, yet could be described only as exaggerated vesicular breathing.

Specific Diagnostic Tests

Throat washings obtained from all 30 patients were cultured in embryonated eggs. Fourteen such specimens were found to contain Asian strain of influenza virus. Paired sera, as determined by hemagglutination inhibition antibody studies, were diagnostic of the Asian strain in 27 of these 30 patients. In addition, the virus was recovered from culture of tracheal material obtained at bronchoscopic biopsy in two of nine patients.

Roentgenologic Examination: All patients had teleroentgenograms of the chest. In six a pneumonic process was demonstrated which was usually basal (five cases) and bronchopneumonic in distribution. All infiltrates cleared promptly after administration of appropriate antibiotic therapy.

Hematologic Studies: Of 24 patients in whom the erythrocyte sedimentation rate was determined, only three were within normal limits. In only five patients was the total white blood count below 5,000 per cubic millimeter,

and in only three with uncomplicated influenza was it more than 10,000 per cubic millimeter. Four patients with bacterial complications had similar elevation in total leukocytes. Of six with polymorphonuclear leukocytosis, only one had uncomplicated influenza. Lymphocytosis was observed in six patients, all with uncomplicated influenzal infections.

Bacterial Agglutination Reaction: The antibody titer of serum was determined in 15 of the 30 patients, in all of whom it was found to be within normal limits for heterophil, typhoid O, typhoid H, paratyphoid A, Proteus OX-K and *Brucella abortus.* The level of cold agglutinins did not become elevated in the five patients in whom it was determined. In 15 patients in whom serial antistreptolysin "O" titers were determined, no alterations were noted.

Hepatic Function: Approximately two thirds of the 30 patients were subjected to a series of liver function tests, which included cephalin flocculation, thymol turbidity, serum bilirubin partition, total protein and albumin globulin ratios, total cholesterol, alkaline phosphatase, prothrombin time, and excretion of bromsulfalein, all of which were reported to be within normal limits except for the excretion of bromsulfalein in two patients. One of these was an elderly man with Klebsiella pneumonia and a past history of excessive ingestion of alcohol. He had a retention of 12% of the dye at 45 minutes. The other patient with uncomplicated influenza had a retention of 9% at 45 minutes; he did not return for reëxamination.

Renal Function: Measurements of blood urea nitrogen in 15 patients and excretion of phenolsulfonphthalein in 10 patients were reported as normal. Routine urinalysis on admission yielded a 1 plus reaction for albumin in five patients, and a 1 plus reaction for acetone in two patients with pneumonia. Two of the patients with albuminuria also had pneumonia, a third had the nephrotic syndrome, and the remaining two had uncomplicated influenza. Subsequent urinalysis in all patients revealed persistence of albuminuria only in the patient with the nephrotic syndrome.

Bacteriologic Studies: Cultures of blood and of urine were obtained in 15 and eight patients, respectively, with negative results. Cultures of the sputum and of material obtained from the nasopharynx were made in all patients on several occasions. Normal flora were found in all but two with pneumonia; sputum cultures in one yielded *Klebsiella pneumoniae* and in the other innumerable staphylococci. These studies were of the type obtained in routine hospital patient care and do not represent extensive or specially directed bacteriologic investigation, a neglected aspect of hospital studies today.

Cerebrospinal Fluid: Lumbar puncture performed in four patients yielded normal pressure, cells, protein, glucose, chloride and cultures for bacteria and virus.

Serum Enzymes: The serum glutamic oxalacetic transaminase (SGOT) was determined in 20 patients from 36 to 72 hours after the onset of illness

and found to be within normal limits. Similar results were noted when the serum glutamic pyruvic transaminase levels were measured in 11 of these patients simultaneously, and in six patients in whom these determinations were repeated during convalescence. In one patient with uncomplicated influenza, the SGOT measured 60 Karmen units. This patient also had a 45-minute retention of bromsulfalein of 9%. There was no other clinical or laboratory evidence of hepatic disease.

Fluid and Electrolyte Studies in 24-Hour Urinary Specimens: Urinary excretion of 17-hydroxycorticoids and 17-ketosteroids was measured in 17 patients at the height of illness and during convalescence. In two patients only a single determination was made, but the remaining 15 had from two to four such determinations. In every instance the excretion of 17-hydroxycorticoids was within normal limits. In three the excretion of urinary ketosteroids was increased during the 24-hour period at the height of illness. Two of the patients were women with uncomplicated influenza whose peak excretion of 17-ketosteroids was 21.8 and 20.5 mg. in 24 hours, respectively. The third patient was a man with staphylococcal pneumonia who excreted 27.1 mg. of 17-hydroxyketosteroids in 24 hours at the height of his illness. On the following day all values had returned to normal.

In 21 patients determinations of serum sodium, potassium, chloride and osmolarity were obtained on at least one occasion, but usually three or four such examinations were made, beginning at the peak of illness and continuing through convalescence. Simultaneously, sodium, chloride and potassium content and osmolarity of 24-hour urinary samples were found to be normal, except for a slight lowering of sodium excretion in six of 13 patients studied during the height of illness. Serum osmolarity in five of these decreased as much as 10 milliosmols, but all values returned to normal during convalescence. Generally, urinary osmolarity and electrolyte content were low when determined at the peak of illness and increased during convalescence, being reversed in four patients. Carbon dioxide combining power was normal in all patients.

Endobronchial Pathologic Changes: In all nine patients in whom bronchoscopic examination and biopsy were performed at the height of illness, varying degrees of edema, hyperemia, congestion and increased secretions throughout most of the tracheobronchial tree were observed. Specimens obtained by bronchial biopsy were cultured, and Asian strain of A influenza was recovered in two patients. The specimens had a similar microscopic appearance, although the extent and intensity of pathologic change increased the more distal was the specimen in the tracheobronchial passage. Irregular desquamation of the lining epithelium was usually evident, with many scattered areas of transitional type metaplasia (figure 1). Cellular nuclei exhibited pyknosis and variations in size and shape. The basement membrane and the lamina propria were thickened and edematous. Vascular engorgement and inflammatory infiltrate, consisting of lymphocytes, histio-

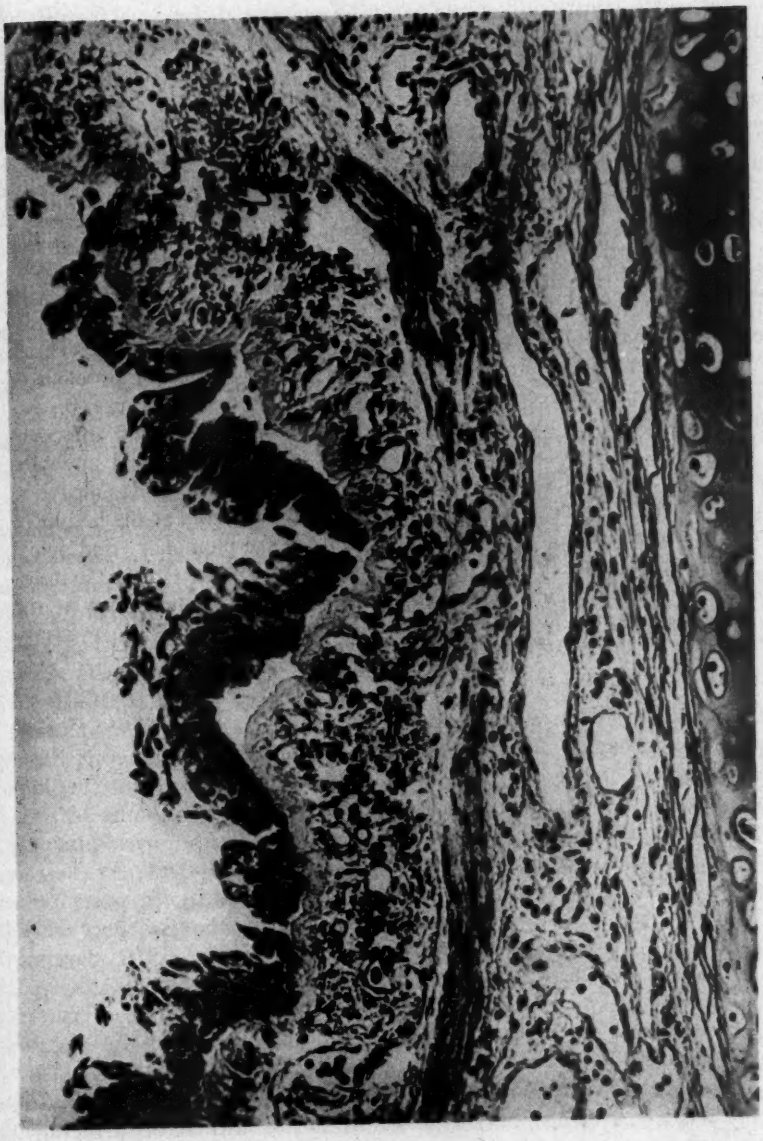

FIG. 1. Photomicrograph of bronchial biopsy obtained from patient with Asian influenza during symptomatic phase of illness (×430).

cytes and plasma cells, with occasional eosinophilic and polymorphonuclear leukocytes, were consistently observed. The elastic tissue was frequently the site of edema, fragmentation, and increased affinity for eosinophilic stains.

Hospital Course

Fever: The total duration of the febrile state was 4.4 days (1.4 days before admission and three days during hospitalization) in patients with simple influenza, and 6.7 days (1.3 days before admission and 5.3 days during hospitalization) in those patients with complicating pneumonia. Slightly more than one third of the patients had a diphasic or "M"-type febrile curve.

Although all patients were extremely uncomfortable, only two with pneumonia appeared to be seriously ill. The first of these was an elderly woman with amyotrophic lateral sclerosis and arteriosclerotic heart disease in addition to her two respiratory infections. When her major problem of evacuating respiratory secretions was overcome by vigorous use of expectorants, wetting agents and bronchodilators, rapid, sustained improvement was noted. The second severely ill patient, a young male, had staphylococcal pneumonia. After two days of intensive antibiotic and supportive therapy he improved rapidly and remarkably. Two patients at the height of their illness had a soft, blowing systolic murmur in the pulmonary and apical areas which was transitory. A third patient with previously known arteriosclerotic heart disease had many premature ventricular contractions at the time of admission to the hospital, but these disappeared in a day.

Treatment

Six of the 24 patients with uncomplicated influenza received antibiotics, which did not appear to alter the course of their infections. Three of these six were pregnant, one of whom had beta hemolytic streptococcal pharyngitis.

Two patients with pneumonia were treated with 600,000 units of procaine penicillin and 0.5 gm. of streptomycin every six hours. In addition to this regimen, a third patient with pneumonia received 100 mg. of Terramycin parenterally every six hours, and the one with Klebsiella pneumonia received 0.5 gm. of streptomycin and 500 mg. of tetracycline four times daily. The fifth patient with pneumonia was treated with 250 mg. of tetracycline every six hours. A sixth patient with staphylococcal pneumonia received 600,000 units of procaine penicillin and 500 mg. of erythromycin every six hours, supplemented on the first three days of hospitalization by 400 mg. of chloramphenicol and 40,000,000 units of penicillin, both given intravenously, and probenecid. Patients with complicating pneumonia usually responded favorably within 24 to 48 hours after institution of antimicrobial therapy. Pulmonary infiltrates cleared promptly.

Pulse Rate: The pulse rate normally varies from 70 to 80 beats per minute with a body temperature of 98.6° F., and increases about 10 beats per minute with each degree of elevation in body temperature.[1, 2] Whenever

the pulse rate was more than 10 beats per minute slower or faster than the value predicted on this basis, tachycardia or bradycardia was considered to be disproportionate.

Tachycardia: Twelve (40%) of the 30 patients had 38 episodes of tachycardia, the rate ranging from 14 to 38 (median, 20) beats per minute more than would have been expected from body temperature. All episodes occurred during convalescence. Because of the many nonspecific causes of tachycardia, it is difficult to assign definite significance to these findings. However, it is interesting that 10 of the 12 patients who exhibited tachycardia also experienced bradycardia.

Bradycardia: Twenty (66.7%) of the 30 patients experienced at least one instance of disproportionate bradycardia, a total of 54 such episodes having been recorded. All occurred during the first 48 hours of hospitalization and almost invariably only when the patient was febrile. The median pulse deficit was 18 (range, 12 to 60) beats per minute.

Blood Pressure: Alterations in blood pressure were evaluated in the light of the patients' previous hospital records and convalescence. Convalescence resulted in stabilization of blood pressure at a constant level, probably as a result of bed-rest and restricted activity. Hypertension was noted in five patients, in three of whom it was observed when anxiety and pyrexia were most pronounced during the first 24 to 48 hours of hospitalization, at the height of the patient's illness. The systolic blood pressure was slightly elevated (10 to 15 mm. Hg), with little or no change in the diastolic pressure. During the same period of their illness, the other two had slightly greater alterations, i.e., the systolic pressure rose 15 to 20 mm. Hg and the diastolic 10 to 20 mm. Hg.

Only one instance of hypotension was observed, in a young man who was severely ill with staphylococcal pneumonia. At the time of admission his blood pressure was 120/50 mm. Hg while he lay supine. On sitting he complained of faintness, at which time his blood pressure was 95/40 mm. Hg, and his pulse rate 124 beats per minute. During the next 24 hours his systolic pressure remained around 120 mm. Hg, and his diastolic pressure ranged from 30 to 60 mm. Hg. Throughout the remainder of hospitalization his systolic pressure ranged from 100 to 110 and his diastolic pressure from 60 to 70 mm. Hg. This was the only patient in whom a rheoplethysmogram, obtained at the height of illness, revealed peripheral vasodilation and increased digital blood flow. The decline in arterial blood pressure was therefore due in part to peripheral vasodilation.

Respiratory Rate: Twenty-four (80%) of the 30 patients had no remarkable alteration in respiratory rate at any time during hospitalization. Of the six patients with tachypnea, only four complained of dyspnea. In all six the respiratory rate was approximately 50% greater during the first 72 hours of observation (27 to 30 respirations per minute) than during the remainder of hospitalization (18 to 20 respirations per minute). The tachypnea gradually subsided during the first three days of hospitalization.

Two of these patients had uncomplicated influenza. One complained of dyspnea. A young man with chronic allergic bronchial asthma complicated by the influenzal infection obtained relief of his dyspnea after the use of expectorants and bronchodilators. The remaining three patients with tachypnea had complicating pneumonia. Two complained of dyspnea, and

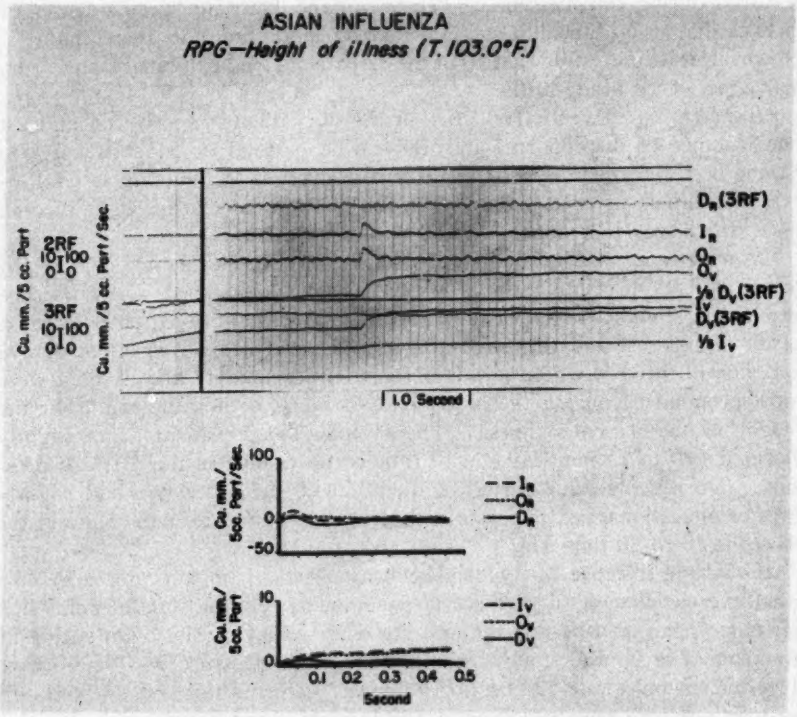

FIG. 2. Rheoplethysmogram of right index finger (2RF) and right middle finger (3RF), recorded simultaneously, in a patient with Asian influenza. I_V, O_V and D_V represent volumes of inflow, outflow, and difference between inflow and outflow, respectively, for 2RF. Similarly, I_R, O_R and D_R represent rates of inflow, outflow, and difference between rates of inflow and outflow, respectively, for 2RF. D_V and D_R for 3RF are also shown. Simultaneous time course curves, showing temporal relations of the volumes and rates of digital blood flow, indicate vasoconstriction of digital circulation. The upper sets of tracings are actual recordings. Enlargements of the rate and volume curves for a single pulse cycle in the upper sets of tracings have been transposed to the two lower groups of curves.

one was slightly cyanotic on admission. None of the patients required oxygen, and none experienced respiratory distress from cardiovascular causes.

Circulatory Studies: The circulation time and venous pressure, determined on at least one occasion in 12 patients, were within normal limits.

Rheoplethysmograms: Twenty of the 30 patients with Asian influenza were studied rheoplethysmographically by the method previously described.[8] In 16 of these patients the diagnosis of influenza was confirmed by serial hemagglutination studies or isolation of the virus. Recordings were made for the right index fingertip at the height of the patients' illness (except in two instances), during convalescence, and several weeks later, after full recovery. All recordings were obtained while the patients were resting in a

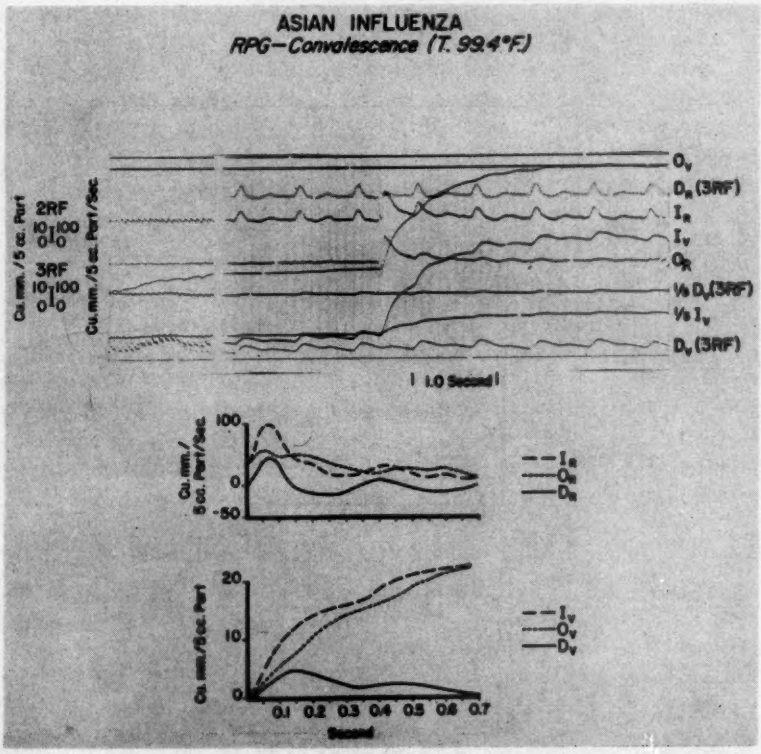

FIG. 3. Rheoplethysmogram of the same patient shown in figure 2, taken during convalescence. Time course curves indicate that the digital vessels are less constricted. See legend of figure 2 for explanation of symbols.

hospital bed in a room with controlled atmospheric temperature and humidity (78° F., 46% relative humidity).

Typical rheoplethysmograms are shown in figures 2, 3 and 4. Fifteen of the patients had decreased digital flow during the height of illness, as evidenced by the time course curves of volume, rate and acceleration in rates of inflow, outflow, and difference between inflow and outflow. The magnitude of the pulse wave and of the alpha deflections was reduced. As the patient

improved, the rheoplethysmograms (RPG) exhibited an increase in digital blood flow, with final normal digital rheoplethysmographic patterns present on full recovery of the patient.

Of the five patients without evidence of reduced digital blood flow, one was only mildly ill clinically, one had a definitely greater rate of flow at the

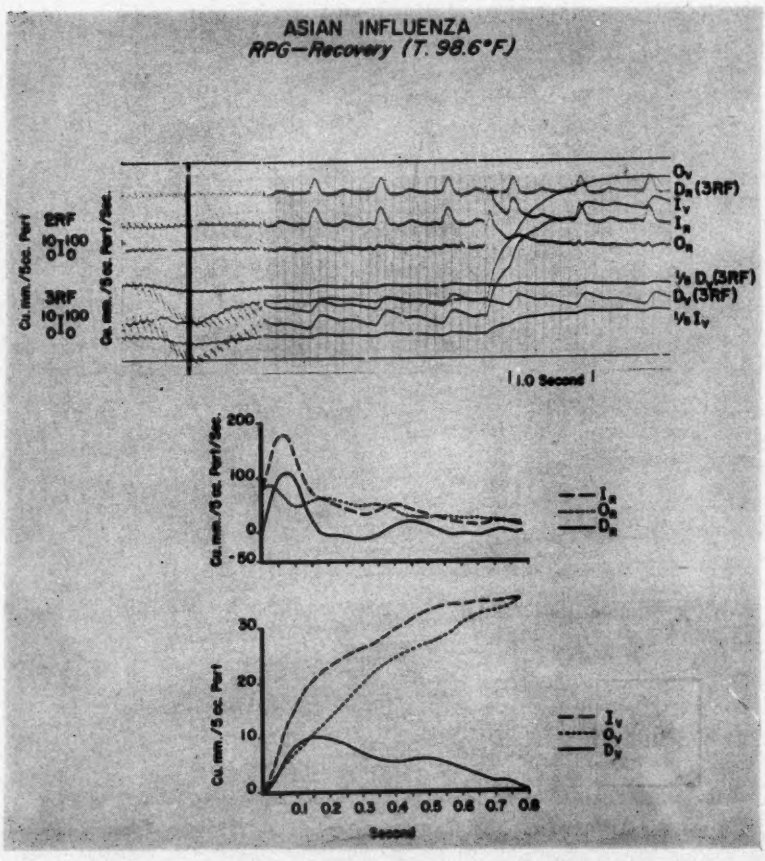

FIG. 4. Rheoplethysmogram of the same patient shown in figure 2, taken during recovery. Time course curves reveal normal digital vascular tone, with considerably more rapid rates of digital blood flow. See legend of figure 2 for explanation of symbols.

height of illness, and in the other no change was noted. In general, the degree of reduction in rate of digital flow appeared to be well related to the severity of illness. The RPGs of three patients with influenza complicated by pneumonia were similar to those of patients with influenza alone.

The percentile change in digital volume, pulse volume and rate of digital

flow in response to a deep breath and to the ringing of a bell was as would be expected for normally innervated and functioning digital vessels. Obviously, the absolute magnitude of change was less when the digital vessels were constricted during the height of illness.

Although the mechanism of the digital vasoconstriction is not known, it may have been related in part to the febrile state associated with any infection. The vessels of the skin tended to constrict while body temperature was rising and fever was developing. These rheoplethysmographic studies indicate constriction of arterioles and arteriovenous anastomotic vessels, but no increase in digital venous tone or venous constriction.

The studies of course did not permit an estimation of the general extent of the vascular response but did show that the disease influenced the peripheral circulation. Unfortunately, there was no opportunity to study a patient with circulatory collapse or "shock." An interesting subject for speculation was the possible relation of the changes in digital circulation to the severe respiratory and circulatory dysfunction and distress precipitated in patients with cardiac disease by severe influenzal infections. Conceivably, constriction of the superficial vessels of the body could displace excessive quantities of blood into the pulmonary vascular bed, to produce a clinical picture of "acute left ventricular congestive heart failure" or acute pulmonary congestion and edema. This would be analogous to what happens when a patient with severe mitral stenosis walks into a body of water to swim and the increasing pressure of the water displaces more blood into the lungs as he walks into deeper water. This phenomenon is of course independent of changes in the circulation produced by direct myocardial and vascular damage by the virus of influenza.

Electrocardiographic Observations

In this group of 30 patients, 110 standard electrocardiograms were obtained serially. In patients with preëxisting cardiac disease, hospital records provided additional preinfluenza control tracings, but in the remainder only electrocardiograms obtained during hospitalization for influenza were available. From two to five electrocardiograms were obtained simultaneously, with spatial vectorcardiograms in the 20 patients hospitalized for investigative purposes. Serial electrocardiograms were obtained in 16 of these patients with proved Asian influenza, of which 13 manifested abnormal changes. Abnormalities were also noted in the electrocardiograms of two of four patients in whom the diagnosis could not be confirmed by specific virologic procedures.

Two or more standard electrocardiograms were recorded in the other 10 of the 30 patients of Group 1. These 10 were chosen from a group of 36 hospitalized patients with routine electrocardiograms in whom the diagnosis of Asian influenza was established by recovery of the virus or at least a fourfold rise in hemagglutination inhibition antibody, or by both criteria. Ten

of 36 (28%) of the patients had abnormal routine electrocardiograms. Four of the abnormal electrocardiograms were found among 10 patients with influenza complicated by pneumonia, and the remaining six among the 26 patients with uncomplicated influenza.

Not a single instance of impairment of conduction was observed, although Hamburger [4] considered this to be pathognomonic of influenzal myocarditis. Egedy [5] attributed 50% of postinfluenzal cardiac disorders to lesions of the conduction system. Alterations in T waves were common. In the standard electrocardiograms of 23 of the 30 patients examined, temporary T wave

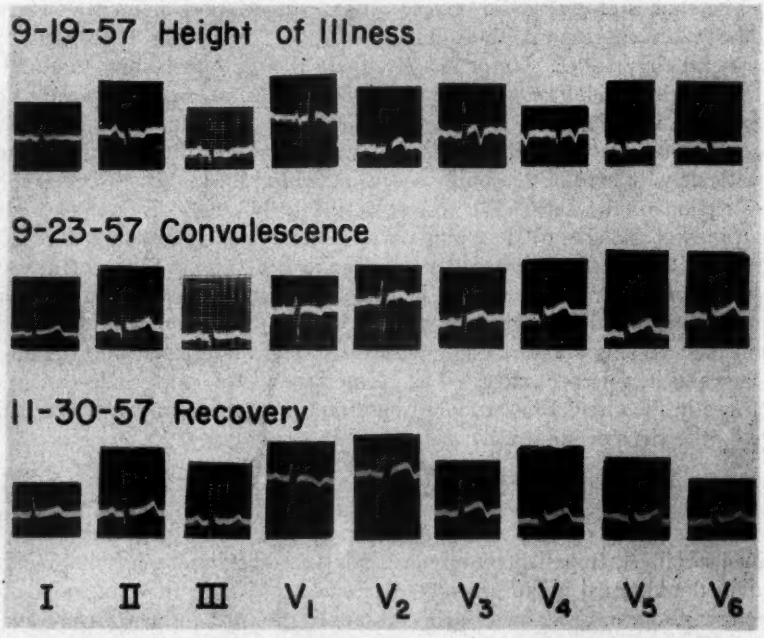

FIG. 5. T wave changes in a patient, 18 years of age, with Asian influenza at peak of illness. These disappeared when the illness subsided.

changes were noted (figures 5 and 6). In nine of these the T wave was inverted or diphasic in one or more leads, whereas in the other 16 it was significantly lowered or iso-electric.

The manifestations were limited to, or most prominent in, precordial leads V_4 through V_6, although in approximately one-half of each of the foregoing groups the standard leads had similar changes. The degree of electrocardiographic abnormality varied considerably, but changes were usually most obvious at the time of admission and disappeared with convalescence. Occasionally the tracing returned to normal within 24 hours.

Abnormalities were noted in the electrocardiograms of five patients in whom reëxamination was impossible.

It is not possible to evaluate the significance of these observations. Of all the components of an electrocardiogram, the T wave is the most labile, and its aberration is nonspecific. Levine [6] listed 67 factors affecting T waves, including 18 infectious processes, but he did not include influenza.

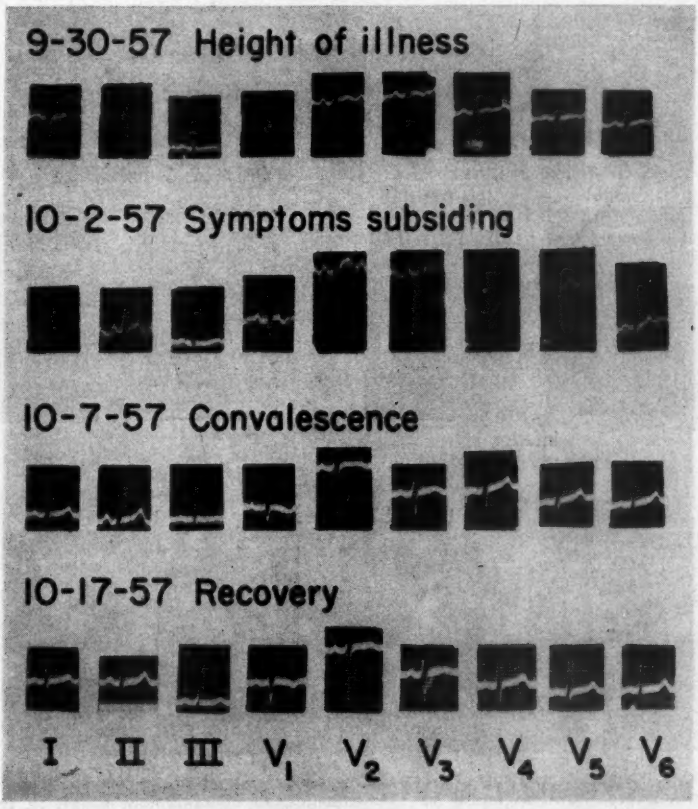

FIG. 6. Alterations in T waves in patient, 22 years of age, with Asian influenza at height of illness promptly disappeared with convalescence.

Nevertheless, it is apparent that influenza can result in anatomic or functional disturbances of the myocardium. Accordingly, any T wave changes incident to influenza may be primary or secondary in origin. These alterations in the order and time course of repolarization were undoubtedly related to the influenza, but not necessarily to specific involvement of the myocardium by the virus.

One patient was noted to have sinus bradycardia (48 beats/min.).

Another had minimal depression of the ST segment in standard and unipolar precordial leads. In one patient the P waves recorded at the height of illness were unusually prominent, but these returned to normal limits during convalescence. Another patient manifested an abrupt shift from right to left axis deviation with convalescence. Neither patient had clinical evidence of cor pulmonale or vectorcardiographic abnormalities, but at the height of illness both had digital vasoconstriction noted rheoplethysmographically. It

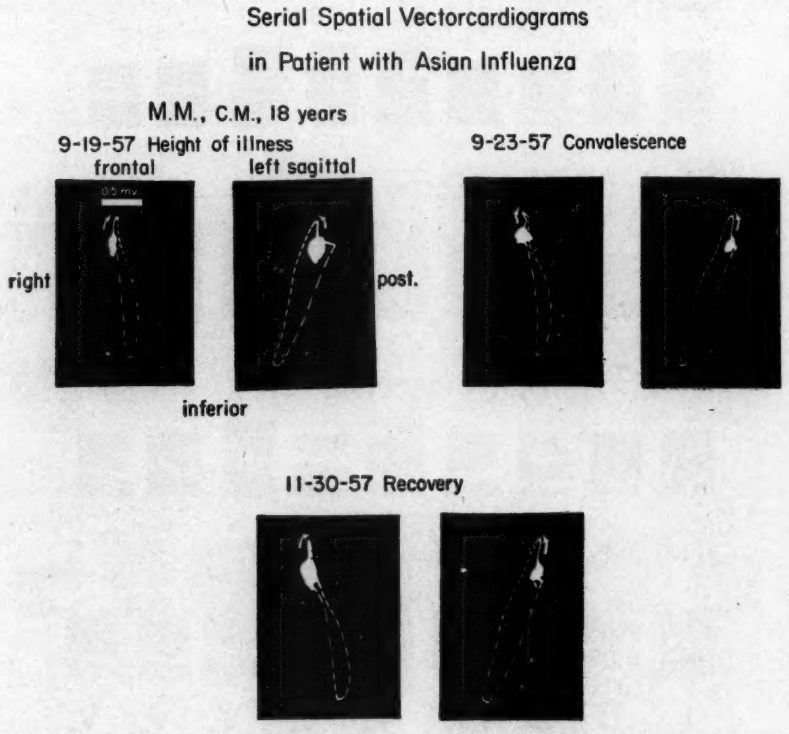

FIG. 7. Normal serial spatial vectorcardiograms of patient whose corresponding electrocardiograms are shown in figure 5. The scale for all views is that shown in the first tracing.

is tempting to postulate pulmonary as well as peripheral vascular spasm in these patients, or displacement of blood to the lungs by diffuse systemic vasoconstriction, or both these phenomena.

SPATIAL VECTORCARDIOGRAPHIC OBSERVATIONS

In 20 patients 60 serial vectorcardiograms were recorded, with the use of the equilateral tetrahedron as a reference frame at the same time as the

standard limb and precordial electrocardiograms.[7] In four instances the tracings were well within normal limits (figure 7). In each of the remaining 16, distortions of the QRS sÊ-loop were noted, resulting in traces that were not so smooth in contour as those usually encountered in healthy young adults. These aberrations or irregularities in contour of the QRS sÊ-loop usually represented mild deformities (figure 8). They may reflect alterations in depolarization, produced by subtle injury, which are not detectable

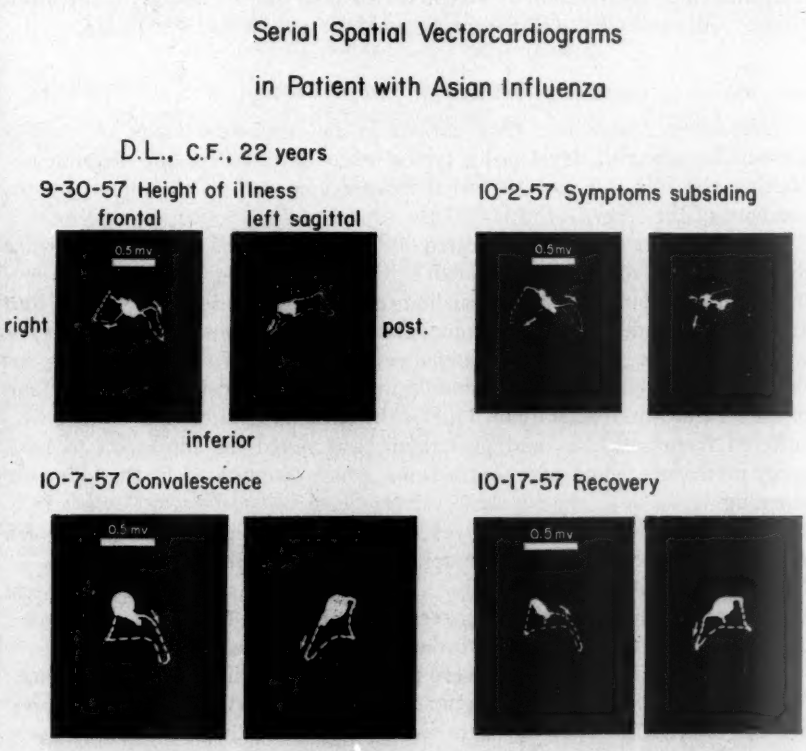

FIG. 8. Serial spatial vectorcardiograms of patient whose corresponding electrocardiograms are shown in figure 6. Note irregularities in contour and diaphragmatic arching of afferent limb of QRS sÊ-loops, which became less prominent with convalescence.

in the conventionally recorded electrocardiogram. In six instances these abnormalities disappeared with convalescence. In the remaining 10 cases the absence of change on serial examination could represent preëxisting changes or a residual of the influenzal infection.

The afferent limb of the QRS sÊ-loops of four patients at the peak of illness exhibited slight arching similar to that observed in diaphragmatic myocardial infarction (figure 8). These distortions disappeared with con-

valescence and are consistent with alterations in depolarization of the diaphragmatic wall of the myocardium. The sVCG suggested slight right ventricular hypertrophy or dilatation, or both, in these four patients.

Complications

In the group of 30 patients, six had pneumonia and one each had purulent conjunctivitis, beta hemolytic streptococcal pharyngitis, and purulent bronchitis. All responded well to conventional therapy, with no sequelae.

Associated Conditions

Nephrotic Syndrome: One patient in the nephrotic stage of chronic glomerular nephritis developed a typical uncomplicated episode of influenza. Neither the infection nor the renal disease appeared to be altered by the presence of the other.

Cardiac Disease: Uncomplicated influenzal infection caused no cardiac difficulties in a 37 year old woman with long-standing compensated rheumatic mitral insufficiency and cardiomegaly. Two patients in the seventh and eighth decades of life had compensated arteriosclerotic heart disease, of whom one was receiving maintenance doses of digitalis. Although influenza was complicated by pneumonia in both of these, neither had worsening of their cardiovascular status. One of the patients with cardiac disease who suffered from influenza and pneumonia was noted on admission to have many premature ventricular contractions, which disappeared by the following morning.

Neurologic Disorders: A 63 year old white woman who had had known amyotrophic lateral sclerosis for approximately one year suffered from influenza complicated by pneumonia. Although she was seriously ill and had considerable difficulty in clearing secretions from her tracheobronchial tree, she responded to chemotherapy, bronchodilators and expectorants.

Pregnancy: Three patients were pregnant at the time of their influenzal infection. In two of these pregnancy was unaffected, terminating several months later in normal, full term infants. One of these patients suffered from complicating pneumonia, which rapidly responded to antibiotic treatment. The third patient, during the course of an influenzal infection, experienced an uncomplicated labor and successfully delivered, spontaneously, a normal, full term infant.

Bronchopulmonary Disease: One patient in this series had bronchial asthma. As previously noted, early in the course of influenzal infection he was moderately dyspneic and had generalized rhonchi and wheezes, which responded to expectorants and bronchodilators.

One of the patients with influenza complicated by pneumonia had a past history of chronic pulmonary disease, including lipoid granuloma treated by right middle lobectomy. At that time, pulmonary function was found to be

consistent with mild ventilatory deficiency. Similar studies performed during convalescence from the influenzal infection showed essentially the same functional state. Although the patient had complained of exertional dyspnea postoperatively, he appeared to tolerate the superimposed respiratory infections without difficulty or significant dyspnea.

Group 2

Patients with Influenza Complicated by Clinically Significant Cardiovascular Disturbances

Four patients experienced clinically significant cardiovascular complications of Asian influenza. Their manifestations are briefly described in the following report of cases.

Case Reports

Case 1. A 36 year old white woman was known to have had rheumatic heart disease for at least 20 years. Because of dyspnea, hemoptysis and serious reduction in exercise tolerance, a mitral valvulotomy had been performed in 1952, after which she had been reëxamined regularly. Although she did well for five years postoperatively, dyspnea, orthopnea and weakness recurred during the middle of 1957. In September of the same year, several days after exposure to influenza at home, she became acutely ill with fever, chills, pains in the chest, myalgia, and cough productive of small amounts of mucoid material. During the next few days she noted a pronounced increase in dyspnea and orthopnea, and the appearance of cyanosis of the lips and nailbeds. She was unable to sleep or to engage in any physical activity because of dyspnea, and she suffered at least two moderately severe episodes of acute pulmonary edema.

At the time of examination in the cardiac clinic she was dyspneic and mildly cyanotic and had slight venous distention and bilateral basal crepitant râles. On auscultation, murmurs of mitral insufficiency and mitral stenosis, with a loud opening mitral snap, were heard. The patient was immediately hospitalized, although it appeared that the worst of the illness had passed. With bed-rest, supportive care, and maintenance of digitalis therapy, she improved rapidly and was discharged in a few days. Incidentally, a second (open cardiotomy) commissurotomy was performed in February, 1958, with use of the DeWall artificial pump oxygenator, but the patient died several hours later.

The diagnosis of Asian influenza was made by virtue of a fourfold or greater rise in hemagglutination inhibition antibody titer of paired sera obtained for this patient. The influenza did not seem to contribute to her death, which was apparently caused by open cardiotomy.

Case 2. A 38 year old Negro woman with known rheumatic mitral stenosis since 1950 had never experienced cardiac symptoms before her influenzal infection. Several days after exposure to influenza, chills, fever, cough and headache suddenly developed. On the second day of illness, dyspnea and orthopnea appeared. On the following two or three evenings she had paroxysmal nocturnal dyspnea and coughed up copious amounts of frothy pink sputum.

At the time of admission, on about the fifth day of illness, her temperature was 99° F.; pulse, 88; respiration, 24. Slight cervical venous distention, basal crepitant râles bilaterally, and cardiomegaly were evident. Signs of mitral stenosis were noted on auscultation. Venous pressure was 210 mm. of water, and the circulation time was 19 seconds. Other laboratory data were not remarkable.

The patient was treated with bed-rest, restricted intake of salt, and mercurial diuretics. She lost eight pounds of edema fluid overnight and became asymptomatic. All evidence of congestive heart failure disappeared, and the patient was discharged without further medication. On reëxamination two months after discharge, she was asymptomatic and had no evidence of cardiac insufficiency. The diagnosis of Asian strain influenza was made by more than a fourfold rise in the hemagglutination inhibition antibody titer on examination of paired samples of serum.

Comment: These are the only two influenzal patients who had rheumatic mitral stenosis. One additional patient with isolated mitral insufficiency tolerated the influenzal infection without difficulty.

That patients with rheumatic heart disease and mitral stenosis may experience particular difficulty when stricken with influenza is evident from the foregoing reports. However, the specificity of influenza is not absolute. Thus case 1, after recovery from influenza, had been closely observed and frequently hospitalized incident to evaluation for a second commissurotomy. During one such hospitalization an undifferentiated respiratory infection of moderate intensity precipitated pulmonary edema. Conversely, the other patient, since recovering from influenza, has had no difficulty with at least one moderately severe upper respiratory tract infection.

Increased metabolic demands of the febrile state result in increased cardiac work actually in excess of need.[8] The already diseased myocardium may be more vulnerable even to mild myocardial injury produced by influenza. Anxiety and pain also contribute to the demands on the cardiac reserve. These factors, common to all infectious processes from which the patient with mitral stenosis suffers, assume importance only in accordance with the state of cardiac reserve. Thus, any moderately severe infection in a patient with mitral stenosis and sufficient impairment of cardiac reserve or a critically reduced mitral orifice can produce cardiac insufficiency. This was probably true in case 1.

Are there unique features of influenza that are specifically detrimental to patients with mitral stenosis? Increased liability to secondary infection, as a result of extensive destruction and alteration of the respiratory mucosa, is a significant feature. The endobronchial secretory mechanism may be inadequate for several weeks, awaiting regeneration of mucus-producing and cilia-bearing cells.[9] Pulmonary vascular as well as systemic vascular damage may occur in the form of pulmonary arteritis and phlebitis, which may result in pulmonary emboli. Frequently, thrombi are found in the vessels of the lung. Characteristically, interstitial emphysema, pronounced vascular engorgement, and diffuse pulmonary and bronchial edema were noted at postmortem examinations.[10] All of these factors impair oxygenation and produce pulmonary arterial and arteriolar constriction and pulmonary hypertension, vascular damage and edema. In a vascular system that is already the site of hypertension, with a limited escape orifice and taxed by increased demands in the presence of limited reserve, these may constitute an unbearable burden. Such a problem, which confronted Sansom [11, 12] more than 60

years ago, continues to threaten the patient with mitral stenosis who contracts influenza.

Case 3. A 20 year old Negro woman, gravida II (expected date of confinement, the day of admission), was hospitalized because of dyspnea. On the day preceding admission she had begun to experience malaise, and several hours before admission she noted the sudden onset of chills, fever, headache, cough and retrosternal aching. Shortly thereafter she became extremely dyspneic and sought hospitalization. Her past history was significant only in that she had had four or five mild asthmatic attacks during the preceding five years.

On physical examination at the hospital on September 9, 1957, this acutely ill, dyspneic woman had a temperature of 101.8° F.; respiration, 28; pulse, 126; blood pressure, 128/78 mm. Hg. The nasopharynx and conjunctivae were injected. Generalized rhonchi with inspiratory and expiratory wheezes were audible, and questionably crepitant râles were heard in one pulmonary base. Teleroentgenogram of the chest was consistent with bilateral patchy basal pneumonia. Cultures of blood and sputum failed to yield pathogenic bacteria. With the exception of a white blood count of 13,500, with 88% polymorphonuclear leukocytes, results of extensive laboratory studies were negative. Paired sera, spaced two weeks apart, revealed greater than a fourfold rise in hemagglutination inhibition antibody titer against Asian strain of influenza. Routine electrocardiograms were within normal limits.

The patient was treated with expectorants, bronchodilators and antibiotics, consisting of 600,000 units of procaine penicillin, 0.5 gm. of streptomycin, and 100 mg. of Terramycin, given parenterally at intervals of six hours. She appeared to improve within the next few hours and experienced a spontaneous four-hour labor, which terminated in the spontaneous delivery of a normal, full term infant. Almost immediately after delivery her clinical state deteriorated remarkably, with extreme dyspnea (60 to 64 respirations per minute), cyanosis, a pulse rate of 156 beats per minute, and generalized crepitant râles, rhonchi and wheezes. Her skin felt cold and clammy, and her blood pressure was 110/58 mm. Hg. In addition to intravenous digitalization, she was treated with oxygen, Demerol hydrochloride, bronchodilators, expectorants and Alevaire. Administration of parenteral cortisone was begun. Within several hours the patient showed remarkable improvement and became practically asymptomatic within several days. All medications were discontinued, and the patient was discharged from the hospital on September 20. Reëxamination two months later elicited no complaints or abnormalities.

Comment: This case demonstrates the problems that may be presented by pregnant patients who contract influenza. She had never had any serious previous illness, yet within 24 hours of the appearance of the first symptoms of influenza she almost died. At the height of her illness she appeared to be suffering from acute pulmonary edema. Energetic therapy was effective, and no residual damage was observed.

Case 4. A 19 year old Negro woman had had attacks of rheumatic fever in January and May, 1957. No residua were apparent, and the patient was asymptomatic until shortly before admission in August, 1957. Although she had not been faithful in taking prophylactic antibiotics, she was well until five days before admission, when she noted the onset, over a period of two to three days, of fever, sore throat and retrosternal aching malaise. During the 36 hours before hospitalization she became increasingly dyspneic and experienced bilateral pleuritic pain. She admitted general, but denied specific, contact with influenza.

On physical examination this acutely ill, dyspneic girl had an oral temperature of

106.2° F.; blood pressure, 110/80 mm. Hg; pulse, 140. The nasopharynx was injected and the cervical veins were distended. On examination of the chest, definite cardiomegaly and pericardial friction rub were evident, as well as bilateral dullness, increased breath sounds, and crepitant râles in the pulmonary bases. A questionable pleural friction rub was noted in the left axillary region. The venous pressure was 220 mm. of water, and the circulation time was 15 seconds.

Teleroentgenogram of the chest revealed cardiomegaly and bilateral pleural effusion. Examination of many preparations for cells of lupus erythematosus yielded negative results. The antistreptolysin O titer on admission was 1:50, and two weeks later was 1:100. Examination of paired sera, obtained simultaneously, resulted in more than a fourfold rise in hemagglutination inhibition antibody titer diagnostic of Asian strain of influenza. Serial electrocardiograms contained persistent inversion of the T wave in all standard and precordial leads. Results of all remaining laboratory studies, including blood, sputum and throat cultures, were negative.

The patient was digitalized and received large doses of salicylates. Because of allergy to penicillin she received tetracycline and streptomycin. Although desperately ill on admission she responded promptly to therapy. After six weeks, administration of digitalis was discontinued, and she was discharged to home care. Five months later no abnormalities were found and the electrocardiogram was normal.

Comment: This patient apparently experienced a severe episode of acute rheumatic pancarditis, complicated by congestive heart failure. Evidence of streptococcal infection was meager. The episode may have represented reactivation of rheumatic fever by an undemonstrated streptococcal infection complicating influenza, or smoldering rheumatic activity that manifested itself as a result of the influenzal infection. The entire episode may have represented a spontaneous bout of rheumatic fever in a patient with a significant rise in hemagglutination inhibition antibody titer incident to an asymptomatic influenzal infection. Finally, the cardiac manifestations may have been superimposed upon an old, inactive rheumatic cardiac state. The clinical situation was never fully clarified, except that the influenzal infection seemed to be of considerable importance in producing the cardiac manifestations.

Discussion

As demonstrated by Stuart-Harris,[13] Francis [14] and Horsfall,[15] the clinical characteristics of influenza vary not only from epidemic to epidemic but also within the same epidemic. Variations of many sorts were noted during the influenza pandemics of 1889, 1918 and 1957.[16, 17] The clinical impressions obtained in this study, however, are in essential agreement with those recorded by other observers during previous epidemics and pandemics,[16, 18-22] the main variations being in incidences of symptoms and complications. Specific diagnostic procedures substantiate the nature of the illness with qualification, i.e., specific antibody response may occur without clinical infection, as may recovery of the influenza virus from nasopharyngeal secretions of contacts who remain virtually symptom-free.[23]

It would appear that another medical cycle has been completed. Only a few decades ago, "myocarditis" was probably the term most frequently

applied to describe structural alteration of the myocardium, probably because of overenthusiasm and inaccuracies in concepts and diagnoses. There followed a period during which mere consideration of myocarditis in differential diagnosis required vigorous, almost heroic defense. However, in the last 15 years data have steadily accumulated to substantiate the frequency and significance of myocarditis and myocardial degeneration.[24-28] Undoubtedly, myocarditis is most frequently associated with acute infectious diseases. When a particular search has been made for myocardial involvement in association with infectious processes, a relatively high incidence of myocardial disease has been found, dependent, of course, upon the particular infectious process studied.[29-32] Over a period of years Teloh [33] noted that the incidence of myocarditis in patients who died of poliomyelitis varied from 33 to 66%. Although his series was not large, in one year the incidence reached 100% and raised the question of a viscerotropic strain with predilection for the myocardium. At the other end of the spectrum is the extremely rare instance of tuberculous myocarditis.[34, 35]

According to de la Chapelle and Kossman,[36] pathologic data support an over-all postmortem incidence of myocarditis of 10%, provided adequate postmortem examination is performed on all persons who die of any infectious process.[36] Obviously, however, myocardial involvement could conceivably occur in the absence of demonstrable histologic change.

Occasional cases of myocarditis due to influenza are included in most series of patients with myocarditis as a complication of infectious diseases. However, the generally reported incidence of such cases is low, usually only a few patients. Of course, some of the reported instances of myocarditis after "recent respiratory infection" may well be influenzal in origin. Interestingly, Nisse [37] considered influenza to be probably the most frequent cause of severe involvement of the myocardium, and Hyman [38] estimated that cardiac abnormalities occurred in 5 to 12% of influenzal cases observed in three large cities. From personal observations in the pandemics of 1889 and 1918, Stengel [16] found cardiac and cardiovascular complications and sequelae to be not particularly rare. Hamburger [4, 39, 40] over the course of 20 years, reported postinfluenzal cardiac abnormalities and emphasized that lesions may be structural or functional. He indicated that disorders of the conduction pathways of the heart were as pathognomonic of influenza as mitral stenosis is of rheumatic heart disease. This does not appear to hold for Asian influenza. Burnett [41] included in an electrocardiographic study of 100 cases of acute infection 11 cases of postinfluenzal cardiac disorders. Generally, the reported abnormalities consisted of disturbances in conduction and T wave changes, only a minority of patients experiencing symptoms. Isolated cases of influenzal myocarditis have been reported in the literature.[42-44] Finland [45] reported the first cardiac fatality in which the influenza virus was isolated. In a report of the pathologic changes in 143 fatal cases of influenza during the pandemic of 1918, it was stated that "it was unusual to find a

heart in these cases that could be considered normal." [22] More recently, Silber [46] reported a series of 21 cases of myocarditis and two cases of pericarditis, of which six were associated with significant rise in antibody titer for influenza A and B.

To be sure, all observers do not agree concerning the frequency or severity of cardiac complications.[47-50] Lichty [21] and Aldrich [51] considered postinfluenzal cardiac complications to be infrequent, and Opie,[18] Lucke [52] and Winternitz [10] were not impressed with the pathologic changes in the heart as a result of influenza. Thus, although all observers agree that influenzal infections will damage the myocardium, the incidence or significance remains unsettled.

On the basis of strictly clinical data, the diagnosis of myocardial injury by influenza was not common in this study. Neubauer,[53] on the other hand, made the diagnosis of myocarditis on clinical grounds in more than one-half of 200 patients with acute infectious disease. Fine [54] found that 24 of the 28 patients with electrocardiographic evidence of myocarditis of infectious origin had at least one of the five clinical signs he considered to be consistent with myocarditis: poor quality of the first apical sound, reduction in systolic blood pressure of 20 mm. or more, gallop rhythm, systolic murmur, or pulse rate greater than 125. Both of these observers considered an apical first sound of poor quality to be the most important sign of myocarditis. The incidence of myocarditis varies with the type and severity of the infectious process, the frequency and completeness of observation, and the criteria established at the beginning of a particular study. More than one-half the patients whom Fine [54] believed to have clinical evidence of myocarditis had had either diphtheria or typhoid, both of which are far more serious diseases than influenza. This is substantiated by the death of 11 of the patients. This does not mean, however, that the incidence and severity of myocardial injury after influenza are invariably related to the severity of the attack, for many instances to the contrary exist. Brooks [55] alone has contended that the incidence and severity of myocardial damage are generally related to the severity of the influenzal infection, an opinion that has the appeal of reason.

Thus, a review of the clinical findings in patients in the present study who had electrocardiographic and spatial vectorcardiographic disturbances yielded the following generally accepted clinical suggestions of myocarditis: transitory, soft, systolic, apical murmur (one patient), multiple extrasystoles (one patient), and hypotension (one patient with a transitory murmur also). Disproportionate tachycardia was rare (observed in 12 patients only during convalescence) except in patients who had had disproportionate bradycardia earlier in the course of their illness. This raises the possibility of circulatory instability as a contributing factor in the clinical syndrome, whether constitutional, postinfectious, or related to bed-rest and debility. Regardless of cause, tachycardia as observed in the present study cannot be interpreted

as specifically indicative of myocardial damage. Nor can disproportionate bradycardia observed in 20 patients be considered as clinical evidence of myocarditis. Certainly the evidence in favor of myocardial involvement is more valid, even though bradycardia was limited to the first 48 hours of observation. However, the nature of the bradycardia during the infection also suggests a physiologic response to alterations in function of the autonomic nervous system.

The fact that 15 of 20 patients with influenza had electrocardiographic abnormalities on serial study is not surprising. Similar observations have been made in many other acute infectious processes when, as in the current investigations, a special search was made for such changes. The significance of these alterations in the electrical events in the heart can best be judged by the clinical outcome, but the damage may be extremely subtle.

Spatial vectorcardiograms did not reveal the mechanisms for the electrical alterations. However, the distortion of the QRS sÊ-loop noted in 16 of the 20 patients raises the distinct probability of mild injury not detectable by the ordinary standard electrocardiogram. Evidence of alterations in depolarization, manifested by aberration in the QRS sÊ-loops of four patients, probably indicated delay in depolarization of the basal portion of the myocardium, although the possibility of early right ventricular hypertrophy or dilatation, or both, definitely existed. Temporary prominence of the P wave and transitory right axis deviation in the electrocardiogram, each noted in a single patient, prompt the same conjecture.

The extreme degree of digital vasoconstriction, observed in the rheoplethysmograms of most patients at the peak of illness, was unexpected, even though some vasoconstriction is commonly acknowledged as an accompaniment of rising fever. The RPG further reveals the diffuse cardiovascular effects of influenza and possibly infectious diseases, and indicates the need for studying the systemic pulmonary vessels, as well as the heart, in all types of infections, a neglected field of infectious diseases.

Summary

A series of 30 patients with Asian strain A influenza has been evaluated on the basis of clinical and laboratory data. In 26 of these patients specific diagnostic tests substantiated the diagnosis, the usual reservations in the diagnosis of viral diseases applying. Particular effort was expended in evaluation of the effects of "Asian influenza" on the cardiovascular system. At the height of illness approximately three fourths of the patients had digital vasoconstriction as well as abnormalities of the T wave in the standard electrocardiogram and of the QRS sÊ-loop in the spatial vectorcardiogram. These changes usually disappeared with convalescence.

None of the 30 patients experienced any clinically significant cardiovascular complication of influenza. However, four other patients in whom

the diagnosis was confirmed virologically and who are described in some detail, clearly showed cardiovascular complications of considerable magnitude.

SUMMARIO IN INTERLINGUA

Un serie de 30 patientes con influenza typo A (racia asian) esseva evalutate super le base de datos clinic e laboratorial. In 26 de iste patientes, specific tests diagnostic corroborava le diagnose, intra le limites del usual reservationes in le diagnose de morbos virusal. Un effortio special esseva facite in evalutar le effectos de "influenza asian" super le systema cardiovascular. Al culmine del morbo, circa tres quartos del patientes habeva vasoconstriction digital e etiam anormalitates del unda T in le electrocardiogramma standard e del ansa sE de QRS in le vectocardiogramma spatial. Iste alterationes dispareva usualmente con le convalescentia.

Nulle del 30 patientes experientiava un clinicamente significative complication cardiovascular del influenza. Tamen, quatro altere patientes, in qui le diagnose esseva confirmate virologicamente e le casos de qui es describite in plus grande detalio, monstrava clarmente complicationes cardiovascular de magnitude considerabile.

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INFLUENZA VACCINATION *

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ATTEMPTS to prevent influenza by vaccination began slightly more than 15 years ago. In the winter of 1943–44 a significant reduction in the incidence of influenza A by vaccination was demonstrated in multiple field trials carried out by the Commission on Influenza, Armed Forces Epidemiological Board.[1] Two years later, protection of even higher order was observed with influenza B vaccine.[2, 3] It appeared at that time that the problem of providing a high degree of protection against both influenza A and B might be solved with relative ease. Then, in 1947, influenza A-prime strains appeared, and it became clear that the problem was not a simple one, for the influenza A vaccines in use at that time were essentially ineffective during the A-prime epidemic.[4] During the period from 1947 to 1958, which we may call the A-prime period, a series of field trials with vaccines containing influenza A-prime strains showed again that protection could be obtained which was comparable to or better than that observed earlier with influenza A vaccines.[5, 6, 7] The chief problem remaining to be solved appeared to be that of preparing vaccine which would protect not only against strains current in the past but also against new variants which might appear at any time in the future. This was the situation in 1957 when a new influenza A family, namely, the Asian, appeared in the Far East.[8]

The types of vaccines which have been studied are presented in table 1. In this country vaccines have been prepared from the allantoic fluid of infected chick embryos and the virus has been inactivated. Vaccines have been administered in most studies by the subcutaneous route. There has also been considerable interest in the intradermally administered vaccine and in adjuvant preparations injected by the intramuscular route. Evaluation of vaccine effectiveness can be predicted with some accuracy on the basis of antibody response, for there is good evidence that a high antibody titer is associated with a markedly increased resistance to infection, but definitive evidence of protection can be obtained only in suitably controlled field trials. To date this has been done only with subcutaneously administered vaccine. In passing, it should be mentioned that in other parts of the world live attenuated vaccines administered by the intranasal route have been utilized in preference to the killed vaccines with which we are familiar.

* From the Symposium on Influenza, presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, April 28, 1958.

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TABLE 1

Types of Influenza Vaccine Under Investigation

	Route of Administration
A. Inactivated	
1. Aqueous	Subcutaneous Intracutaneous
2. Adjuvant	Intramuscular
B. Live, attenuated	Intranasal

The situation which existed when Asian strains of influenza A were first isolated appeared to be particularly promising because there was time to prepare in advance a strictly homologous vaccine for the epidemic which was to come. It soon became clear, however, that with Asian vaccines of potency comparable to those used in earlier studies the antibody response to single injections was far less satisfactory than had been anticipated. In retrospect, it is clear that the single injection schedule of immunization which had been followed in the past was unsatisfactory with Asian vaccines because the population had had insignificant prior experience with the dominant antigens of the Asian strain. On the basis of antibody studies (table 2) it was clear that a double or booster type of immunization schedule produced far better antibody response, but time did not permit the utilization of this type of program.

With this background, we will turn to a brief summary of results of certain field trials made during the last year. Several of these were conducted last summer and fall under the auspices of the Commission on Influenza, and all showed essentially similar results. For illustration, the results of studies carried out at Lowry Air Force Base in Denver, Colorado, will be presented.

Two separate studies were conducted, and the experimental design was similar in each (table 3). In the first, vaccine of 200 CCA unit potency was given at the end of July, 1957. In the second, vaccine of 400 CCA unit potency was given on September 24, 1957. Both vaccines were given in single injections of 1 c.c. subcutaneously. Men in study units were divided equally on the basis of the terminal digits of their serial number into a vac-

TABLE 2

Comparison of Asian Hemagglutination-Inhibition Antibody Two Weeks After Administration of Different Vaccines

Potency	No. of Sera*	% with Titer of					% with Titer of 1:16 or More
		<8	8	16	32	>64	
200	45	60	20	14	4	2	20
400	50	20	20	18	28	14	60
200 × 2†	40	0	15	12	30	43	85

* All had titer of less than 1:8 in prevaccination sera.
† Received second injection of same vaccine six weeks after first.

TABLE 3
Outline of Plan of Studies I and II

Study	Vaccine Given	No. of CCA Units of Asian Strain	No. of Men (Oct. 1, 1957)
I*	Monovalent Asian	200	821
	Formalin-saline	—	815
II†	Monovalent Asian	400	616
	Polyvalent Asian	400	540
		Total vaccinated	1,156
	Influenza B	—	605
	Formalin-saline	—	548
		Total control	1,153

* Vaccinated July 29–30.
† Vaccinated September 24.

cinated group and a control group which received an injection of material containing no Asian antigen. The total size of the vaccinated group represented only a small part of the base strength. This provided a relatively small number of vaccinated men in a large pool of susceptibles, and thus placed the vaccine under rigorous test. Follow-up was limited to men who were hospitalized or reported to sick call. Paired blood specimens were collected from almost all the the former and more than one-half of the latter, and were tested by complement-fixation and hemagglutination-inhibition

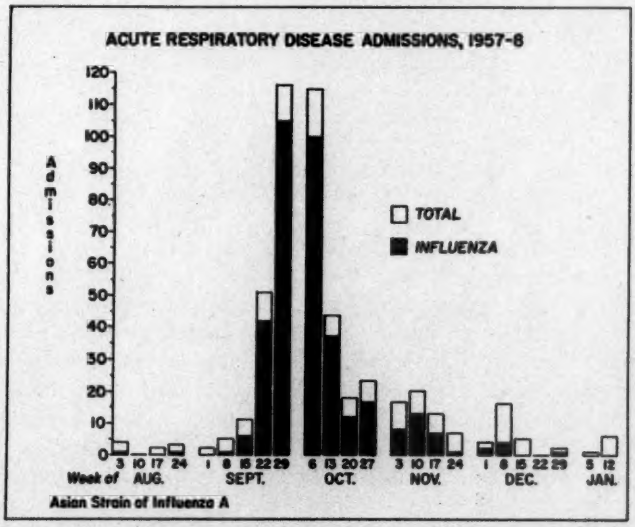

FIG. 1. Number of men admitted by weeks from control groups with influenza and other acute respiratory diseases during epidemic period.

tests. Men were classed as having had influenza or not having had influenza on the basis of serologic tests.[7]

A sharp outbreak of influenza occurred during the latter part of September and October (figure 1). At this time the incidence of other respiratory disease was very low. The epidemic was characteristically sharp, and differed from recent influenza A epidemics only in its somewhat greater duration. During the epidemic period slightly more than 12% of the men on the base were hospitalized with influenza.

Results of the first study are shown in figure 2. Here we see the cumulative number of admissions by weeks from the vaccinated and control groups. It is obvious that there is a difference in favor of the vaccinated group. It is also clear that the incidence of influenza among vaccinated men was appreciable. Results of the second study are shown in figure 3.

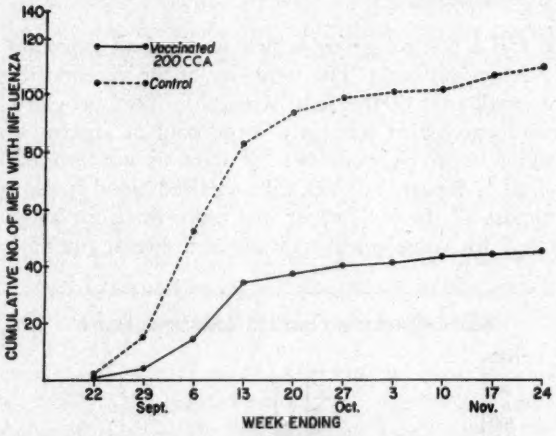

FIG. 2. Cumulative number of men admitted with influenza from vaccinated and control groups in Study I (200 CCA unit vaccine).

It should be noted here that vaccine was given at a time when influenza was already appearing on the base, rather than two and a half months earlier, as in the first study. We see a virtually identical incidence in influenza in vaccinated and control groups during the 10 days following administration of vaccine. Thereafter, a decided difference appears in favor of the vaccinated group. When we consider the period from the tenth day after vaccination onward (figure 4), the evidence of protection seems somewhat greater than that observed in the earlier study. A summary of results of the two studies is shown in table 4. We see here that the protection ratio in the first study was 2.5 to 1, and in the second study, 3.6 to 1.

It is of some interest to compare the results of this field trial with one conducted in January, 1957, during an A-prime epidemic at the same base.[7]

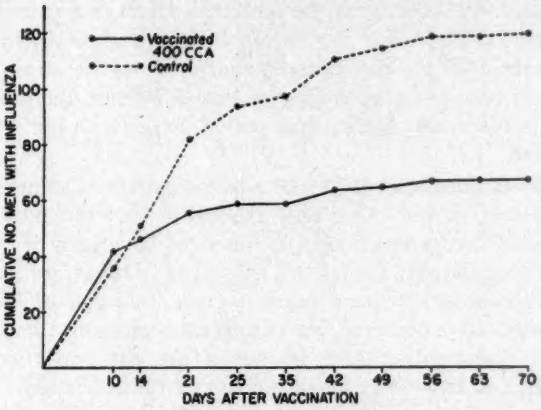

FIG. 3. Cumulative number of men admitted with influenza from vaccinated and control groups throughout period of Study II (400 CCA unit vaccine).

TABLE 4

Summary of Results of Field Trials with Asian Influenza Vaccines

Vaccine Potency	Number of Men with Influenza in		Protection Ratio
	Control Group	Vaccinated Group	
200 CCAU	111	45	2.5:1
400 CCAU*	50	14	3.6:1

* From fifteenth day after vaccination.

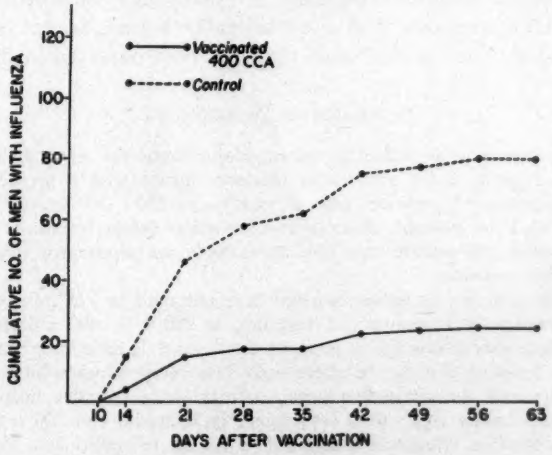

FIG. 4. Cumulative number of men admitted with influenza from vaccinated and control groups following the tenth day after vaccination.

In that study we were measuring the protective effect of a potent monovalent A-prime vaccine (Ann Arbor 56) during an epidemic caused by an A-prime variant (Denver 1–57) which differed sharply from the strain from which the vaccine had been prepared. Despite this difference, the protection ratio was 5.5 to 1, considerably higher than that observed with the Asian vaccines described above.

The results of these studies fit well into the pattern of other studies made during the last 15 years. One may generalize that influenza vaccines in most years, when antigenic changes in the virus have been of minor degree, have provided significant, though by no means optimal, protection against infection. In those less frequent years, notably 1947 and 1957, when major antigenic changes have occurred, the effectiveness of vaccine has been sharply reduced. The most encouraging feature of the last year's experience has been the advance in knowledge about influenza strain variation. The hypothesis that there is only a limited number of major families within the influenza A group has received much support. If it proves true that there is only a limited number of major families of influenza virus, and not an infinite variety of strains, then the problem of protection by vaccination should be solved in the not too distant future.

At present it would appear that the most promising approach to protection against any type of influenza A or B would be to prepare vaccine containing antigens of all the major families of each virus. If there are only four, or possibly five, main families within the influenza A group, this would not be too formidable a task. Following the lines laid out by Davenport, Francis and others,[9] basic immunization against these major families could be provided. Polyvalent adjuvant vaccines are obviously attractive for this purpose. Booster injections of appropriate nature could then be given at suitable intervals, and a considerably higher degree of protection might well be obtained in the future than has been observed in the past.

SUMMARIO IN INTERLINGUA

Inactivate vaccinos de influenza asian, administrate per via subcutanee, esseva evalutate con respecto a lor efficicia in producer anticorpore e provider protection durante un epidemia. Injectiones unic de vaccino de 200 e 400 unitates (de agglutination de cellulas de gallina) evocava relativemente debile responsas anticorporee. Duo injectiones de 200 unitates con un intervallo de sex septimanas produceva multo plus satisfacente responsas.

Durante le epidemia de influenza asian in le autumno de 1957, essayos a controlo esseva interprendite in le campo con vaccinos de 200 e de 400 unitates. Membros del fortias armate esseva dividite in gruppos equal super le base de lor numeros serial. Un medietate recipeva vaccino, le altere medietate recipeva un solution de controlo. Specimens appareate de sanguine esseva obtenite ab le homines hospitalisate, e le diagnoses esseva basate super tests serologic. In le studio con 200 unitates, le proportion del protection effectuate esseva 2,5 a 1. In le studio con 400 unitates, le proportion del protection effectuate esseva 3,6 a 1. Ambe iste proportiones esseva minus favorabile que illo observate in un studio de vaccino de influenza A-un, effec-

tuate in le primavera de 1957. Le rationes de iste relativemente basse nivello de protection es discutite. Es presentate proponimentos pro un plus efficace programma de vaccination contra influenza in le futuro.

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THE EFFECT OF ANTIMICROBIAL DRUGS ON THE STAPHYLOCOCCAL FLORA OF HOSPITAL PATIENTS*†

By VERNON KNIGHT, M.D., F.A.C.P., ARTHUR C. WHITE, M.D., *Nashville, Tennessee,* and MARGARET P. MARTIN, Ph.D., *Syracuse, New York*

AN understanding of the role of drug resistance in current problems with staphylococcal infections will depend in part upon knowledge of the way in which antimicrobial therapy causes drug-resistant staphylococci to develop and persist in hospital patients. Observations in this laboratory suggest that these effects are produced by rather specific mechanisms, and a description of them is the purpose of this report.

THE "REPLACEMENT" PHENOMENON

Hospital patients who are staphylococcal carriers are an essential part of the chain of events leading to hospital cross-infections with drug-resistant staphylococci, for it is by the treatment of these carriers that drug-resistant staphylococci are produced. Once staphylococci have become drug-resistant, they may be acquired by hospital personnel, or other patients, where they will be available to cause staphylococcal infection in susceptible contacts. After a hospital ward has become heavily populated with drug-resistant staphylococci, these strains are perpetuated in the hospital environment by further antimicrobial treatment, to the exclusion of drug-susceptible strains which are brought into the hospital by new patients.

An illustration of the process of perpetuation of drug-resistant "hospital" staphylococci in hospital patients is shown in figure 1, derived from studies at the Veterans Administration hospital in Nashville.[1] It may be seen that at the time of admission to the hospital the patients carried few strains resistant to the tetracyclines, and few of the multiple drug-resistant, phage group III, "hospital" staphylococci which were known to constitute a large proportion of a series of cultures from this ward. After the patients received tetracycline, however, strains susceptible to tetracycline disappeared

* From the Symposium on Staphylococcal Infections, presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, April 29, 1958.

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and were replaced by "hospital" staphylococci. Thus by the seven-to-nine-day period nearly complete replacement had occurred.

We believe that the change resulted from the suppression of the high percentage of tetracycline-susceptible strains by treatment with this drug, leaving the nose and throat and other carrier sites free for implantation with drug-resistant "hospital" staphylococci.

Among patients receiving no treatment the replacement was more gradual, increasing only from 10 to about 30% in a 30-day period. Hospital personnel act in a manner similar to untreated patients in that they acquire drug-resistant strains at a slow rate. For example, Duncan and his associates [2] found that it required 18 months for a shift from 31 to 87% resistant strains in a study of student nurses.

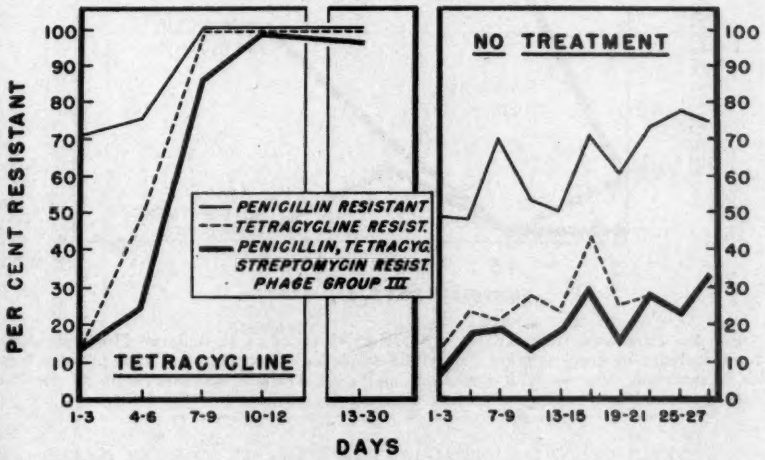

FIG. 1. (Knight and White,[1] reproduced by permission from *Southern Medical Journal.*) Studies at Nashville Veterans Administration Hospital, showing a rapid increase in the proportion of multiple drug-resistant, phage group III, "hospital" staphylococci in cultures from patients treated with tetracycline. There was only a slight increase in the proportion of "hospital" staphylococci in cultures from untreated patients followed for a longer period.

In other studies penicillin was shown to act in a way similar to tetracycline, except that the shift occurred more slowly.[3] This is shown in figure 2, which describes data obtained at Bellevue Hospital from patients treated with penicillin, compared with others who received a tetracycline or no treatment. The slower change in patients receiving penicillin may be explained by the fact that more than 50% of the strains isolated at the time of admission to the hospital were penicillin-resistant. Treatment with penicillin, therefore, suppressed a smaller percentage of the admission strains than did tetracycline, consequently providing less opportunity for replacement with "hospital" staphylococci.

Thus, by means of the "replacement" phenomenon staphylococci of increasing drug resistance are selectively retained in the environment and passed repeatedly from treated patient to treated patient. This is a very intense exposure, and in accord with this observation is the finding that these organisms exhibit resistance to antimicrobial drugs which is greater than can easily be attained by in vitro methods.

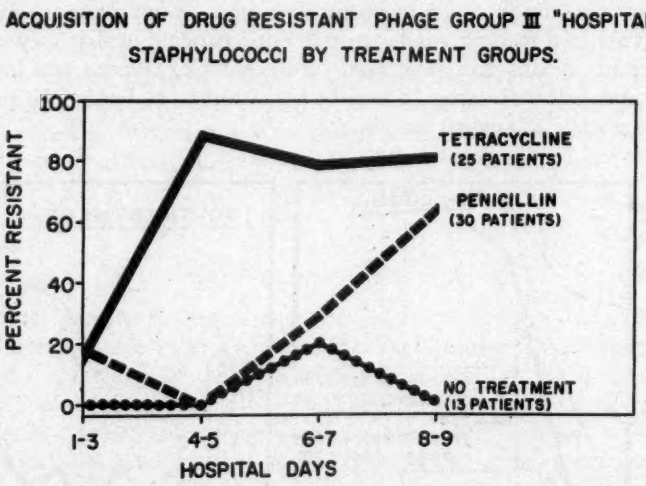

FIG. 2. (Redrawn from Knight and Holzer.[3]) Studies at Bellevue Hospital, showing a rapid increase in drug-resistant, "hospital" staphylococci in cultures from patients treated with tetracycline, less so with penicillin, and only a slight increase with no treatment. (Note resemblance to findings described in figure 1.)

EFFECT OF ANTIMICROBIAL TREATMENT ON CARRIER RATES

It should be emphasized that the preceding data refer to the effect of antimicrobial drugs on persons who were staphylococcal carriers before treatment was started. No evidence has been obtained in our studies that antimicrobial drugs cause the carrier state to develop in noncarriers, and in one study of patients observed for up to 60 hospital days carrier rates in treated and nontreated patients were not significantly different.[4]

As far as we can determine, therefore, the only way antimicrobial drugs influence the numbers of staphylococci carried by patients is to reduce them. This is most easily observed when carriers of susceptible staphylococci are treated with an active drug in an environment also filled with susceptible strains.[5] An example of this is shown in figure 3. In this study erythromycin was given to six carriers in a ward of the mental hospital which contained no strains resistant to this agent. The data presented are the mean of the log of quantitative nasal cultures. After a few days of treatment

the number of staphylococci diminished from several thousand per swab to *all* negative cultures. No change occurred in the colony counts of randomly selected untreated carriers from the same ward, shown by the dotted line in the figure. After treatment was stopped cultures again became positive, and in a three-week period had returned to pretreatment values.

As was demonstrated earlier from studies at the Veterans Hospital, treatment of carriers with an active drug such as tetracycline will cause disappearance of susceptible strains, but if the hospital ward is filled with tetracycline-resistant strains they will implant promptly in the treated carriers to maintain the carrier state.

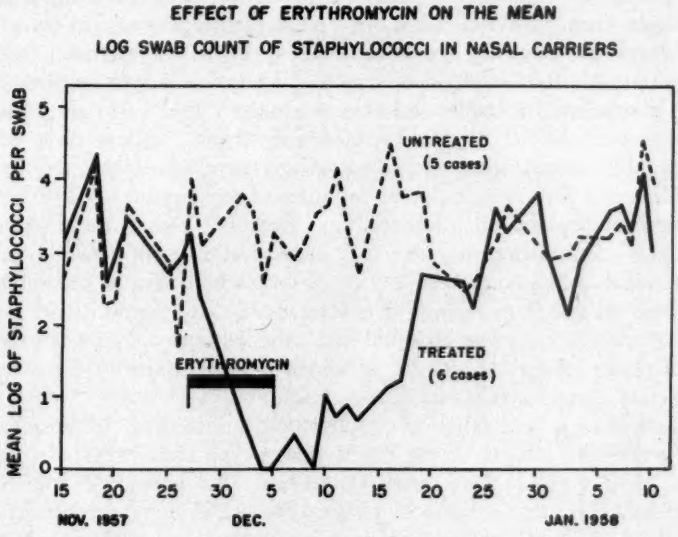

FIG. 3. Erythromycin caused a rapid and complete suppression of the carrier state in six nasal carriers of staphylococci on the wards of the mental hospital at Nashville. Five untreated carriers on the same ward showed no change in their swab counts.

CORRELATION OF DRUG RESISTANCE AND PHAGE TYPES

It has been found that drug-resistant staphylococci are generally lysed by staphylococcal bacteriophages which have been designated as group III, and more recently a trend has been noted of lysis of drug-resistant staphylococci by phages 52, 80, 81, 47C and 42B.[6] These are a mixture of group I and group III phages, and are of patterns quite distinct from the usual drug-resistant, phage group III staphylococci. The explanation has been offered by Barber and Whitehead[7] that staphylococci of these phage groups are genetically unstable and become resistant to antimicrobial drugs more readily than do staphylococci of other phage types.

TABLE 1

Phage Groups of Coagulase Positive Staphylococci from Patient Carriers

Phage Group	Bellevue Hospital, New York, 1953–1954, 516 strains %	Veterans Hospital, Nashville, 1955, 647 strains %	Mental Hospital, Nashville, 1957–1958, 1543 strains %
I	17	14	55*
II	2	13	18
III	75	66	11
Untypable or misc.	6	7	16

* Virtually all phage type: 52, 80 (strong reactions) 81, 47C, 42B (weak reactions).

It should be emphasized that the correlation between drug resistance and certain phage patterns is not absolute, and exceptions have occasionally been observed. Recently we have phage-typed 1,547 cultures (table 1) of coagulase-positive staphylococci from 50 physically well patients at the mental hospital at Nashville, and have made the rather surprising discovery that 55% were of the 52, 80, 81, etc. phage type.[5] About 85% of these were highly susceptible to penicillin and tetracyclines (inhibited by 1 μg per milliliter of penicillin; 6 μg per milliliter of tetracycline). Furthermore, no serious staphylococcal infections have occurred among these patients in recent years, and during this time only occasional doses of penicillin or other antimicrobial drugs have been given. For comparison, in the same table are shown the phage groupings of collections of staphylococci from Bellevue Hospital and the Veterans Hospital in Nashville, both showing a predominance of phage group III strains, of which a large majority were resistant to penicillin, streptomycin and tetracyclines.

The frequent occurrence of staphylococcal infections in hospitals due to drug-resistant strains of the 80/81 phage type has suggested that these strains have greater than usual virulence. The preceding studies have shown, however, that strains of phage type 80/81 may predominate in a hospital ward in the absence of drug resistance, and without appreciable staphylococcal infection.

RELATIONSHIP BETWEEN THE CARRIER STATE AND STAPHYLOCOCCAL INFECTIONS

We have referred to the carrier state in this report as it has been determined by nose and throat cultures. It has been found that skin carriage correlates well with nasopharyngeal carriage. In fact, it appears that the carrier state for coagulase-positive staphylococci is a general body state, of which the nose is a convenient and accurate index. Furthermore, studies of persons with furunculosis and other staphylococcal skin infections [8] have shown that they are almost invariably nasal carriers of the same phage types as those which cause the infection. We have observed a patient with a phage type 47 staphylococcus in his blood and cerebrospinal fluid, as well as

in his throat, nose and rectum.[9] In a number of other patients with localized or systemic staphylococcal infection the nasal cultures have also contained coagulase-positive staphylococci.

These data suggest that it is logical to consider the staphylococcal carrier state as a mild infection, differing from more apparent clinical disease only in severity. The importance of this point is that definite but as yet unknown characteristics of the host apparently determine susceptibility to the carrier state, and it is a good possibility that the same factors increase susceptibility to clinical infections.

The statement that the carrier state is under host control is based on evidence that the carrier state is not randomly distributed in man, and that close exposure of noncarriers to heavy carriers for many weeks does not cause the carrier state to develop with any appreciable frequency. An illustration of these characteristics of the staphylococcal carrier state in man is shown in figure 4.[5]

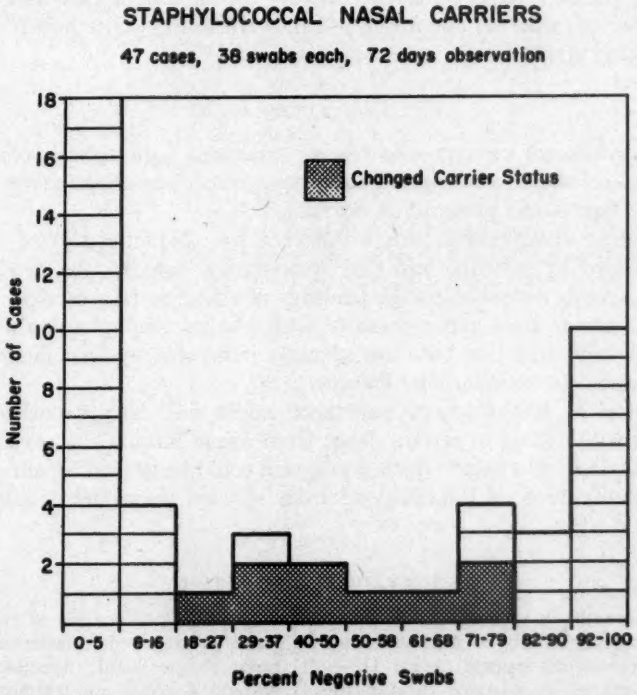

FIG. 4. Almost one-half of a group of patients at the mental hospital in Nashville were persistent carriers of coagulase-positive staphylococci (84% or more cultures positive) for 10 weeks of observation. About one fourth of the patients had cultures almost consistently negative. Nine of 12 patients with 18 to 79% of their cultures negative became persistent carriers or lost their carrier status during the period, so that only three patients were true intermittent carriers.

These data were derived from a study of 47 patients at the mental hospital who had had nasal cultures made three to five times weekly for 10 weeks. It will be observed that 22 (or about one-half) of these patients had coagulase-positive staphylococci present in almost all of their cultures (84% or more). At the other extreme, 13 patients (or about one fourth) had negative cultures most of the time. (Less than 18% of their cultures consisted of sporadic positives.) Among the 12 patients with carrier rates between 18 and 82%, nine either lost their carrier status or became consistently positive carriers during the study, so that only three of the 47 patients were true intermittent carriers.

These cultures were all made by a quantitative technic devised in this laboratory,[5] and it was found that the average number of staphylococcal colonies per swab among the positive cultures of the consistent carriers was about 8,000, whereas the infrequent positive cultures in the "noncarriers" averaged only 300, a highly significant difference. Thus nearly one-half of these patients were persistent carriers throughout a two and one-half month period, whereas about one fourth were nearly continuously negative in the same period in the same hospital ward.

Conclusions

Staphylococcal carriers who receive treatment with antimicrobial drugs are the chief source of drug-resistant staphylococci of phage group III and of phage type 80/81 presently in our hospitals.

Whereas antimicrobial drugs influence the characteristics of staphylococci carried by patients, and may temporarily suppress the carrier state, they apparently do *not* affect the tendency of a host to be a carrier.

The carrier state often coexists with clinical staphylococcal infection, and it is suggested that both are strongly influenced by host factors which are unrelated to antimicrobial therapy.

Control of staphylococcal resistance might well be approached by the periodic withholding of certain drugs from use in hospitals to preserve their antistaphylococcal effect. Such a program could be guided by antimicrobial susceptibility tests of staphylococci from selected personnel or patient-carriers.

Summario in Interlingua

Il pare que in multe hospitales, portatores de staphylococcos qui es tractate con drogas antimicrobial, es currentemente le fonte principal de pharmacoresistente staphylococcos del gruppo phagic III e del typos phagic 80/81. Quando un nove patiente qui es un portator es admittite al hospital e recipe un tractamento antimicrobial, le racias non-resistente dispare promptemente e es reimplaciate per racias resistente ab le ambiente. Portatores qui non recipe un tractamento antimicrobial experientia iste transition plus lentemente e a grados minus pronunciate.

Durante que drogas antimicrobial exerce un influentia super le characteristicas del staphylococcos portate per le patientes e es mesmo capace a supprimer temporari-

mente le stato de portator, illos apparentemente *non* affice le tendentia del subjecto individual de esser un portator.

Le stato de portator existe frequentemente insimul con clinic infection staphylococcic, e il pare probabile que ambes es fortemente influentiate per factores in le subjecto in question le quales ha nihil a facer con le therapia antimicrobial.

Le problema del staphylococcos pharmacoresistente es possibilemente a attaccar per un programma de abstention periodic de certe drogas usate in hospitales, con le objectivo de preservar lor effecto antistaphylococcic. In le execution de un tal programma on poterea guidar se per le execution de tests de susceptibilitate antimicrobial in staphylococcos ab seligite membros del personal o ab patientes qui es portatores.

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THE DISEASE SPECTRUM OF HUMAN HISTOPLASMOSIS*

By Amos Christie, M.D., *Nashville, Tennessee*

I CANNOT be sure at this time that I had ever heard of histoplasmosis when I was invited to assume the Chair of Pediatrics at Vanderbilt in 1943. It was another rare, esoteric infectious disease which I certainly never expected to see unless the academic fates took me to the tropics.

As one interested in pediatrics, and particularly in the chest diseases of children, I was entirely familiar with the problem which existed in a large section of this country, to wit: "The tuberculin test is invalid as an epidemiological index of tuberculous infection." It does not react in hundreds of individuals who have pulmonary calcification—calcification which is occasionally extensive and indistinguishable from the primary complex or multiple healed lesions of tuberculosis. Either the tuberculin test acts differently in Nashville than in New York, San Francisco and Baltimore, or there must be another cause of pulmonary calcification in the southeastern United States and at Vanderbilt. This was the situation in 1943.

About this time I saw my first case of disseminated progressive histoplasmosis. Here was a fascinating infection. According to the textbooks, every case was uniformly fatal. This seemed to me to be without biologic precedent for an infectious disease. I had been raised medically at the University of California and had witnessed the unfolding of the entire problem of Coccidioides and coccidioidomycosis. As a medical student of the late 1920's, Ophuls'[1] name "Coccidioidal granuloma" for the disseminated infections had made a profound impression. Most if not all of the patients died. In 1936–37 it was Dickson and Gifford[2] who showed that a spectacular disease of the San Joaquin Valley, characterized by respiratory infections and erythema nodosum, was also caused by Coccidioides, but was not necessarily fatal. The name "coccidioidomycosis" was given to the disease, and the term included the benign infections as well as the disseminated, progressive variety. The work of my old friend, Charles E. Smith,[3, 4, 5, 6] in describing the clinical picture and working out the epidemiology and immunology of coccidioidomycosis, is well known to almost everyone in the audience. Prodded by Dr. Smith, I felt it was obvious that we must look into the possibility that a benign form of histoplasmosis, similar to that of coccidioidal granuloma, could be the cause of pulmonary calcification in nonreactors to tuberculosis in this geographic area.

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Time does not permit a historical review, which has been done quite accurately by Schwarz and Baum in a recent article in the *New England Journal of Medicine*,[7] but there are several landmarks which would seem to give a background to what follows. Before Darling's [8a] first report in 1906, the disease was apparently unknown. He, of course, felt that it was a generalized protozoan infection which produced proliferated lesions that he referred to as pseudotubercles in the lungs and focal necrosis in the liver, spleen and lymph nodes. In 1926 Watson and Riley [9] in Minnesota reported the first North American case, but it remained for Demonbreun [10] at Vanderbilt University in 1934 to demonstrate conclusively, by brilliant and epochal transmission and culture experiments, the fungous etiology of this infection. The third landmark, of course, as I have mentioned, was in 1945, when the relationship of histoplasmin sensitivity to pulmonary calcification in the nonreactors to tuberculin was demonstrated by us [11] and rapidly confirmed by others.[12] Since that time we have been busy attempting to define this disease spectrum, and it is interesting to note that in a remarkably short time—about 50 years—the etiologic agent has been identified, the pathogenesis of the infection established, the epidemiology worked out, and the clinical picture delineated in many of its variations. Reliable diagnostic tests have been established. Those of us at Vanderbilt are always proud to have the fact noted that many of the major contributions to this knowledge have been made at Vanderbilt by members of its staff, past and present.

Epidemiology of Histoplasmosis

I should like now to summarize what is known concerning the epidemiology. Though the disease is worldwide, more than one-half of the cases reported have appeared in States which correspond to the area of the western Appalachian slope and those bordering the tributaries of the Ohio, Missouri and Mississippi Rivers. The area of endemicity is a pear-shaped one, roughly bounded by St. Louis, Missouri, and Little Rock, Arkansas, at the base, with northern Georgia and Columbus, Ohio, in the middle, as the apex tapers along the upper reaches of the Ohio River. There are many other known foci in Mississippi, Texas, Minnesota, Pennsylvania and upper New York State. Interestingly, and significantly, those are the areas which correspond to the ones in which pulmonary calcification in nonreactors to tuberculin is high. Though little is known about how *Histoplasma capsulatum* gets into the human body, the fungus has been repeatedly found in the soil and has been positively identified in dogs and many other animals. However, there is no evidence of transmission from animal to animal, or animal to man, or man to man. We believe there is probably contamination of the soil with an intermediate saprophytic phase of the fungus, and then infection of man by ingestion or inhalation, or both, of the spore-containing dust or dirt (figure 1).

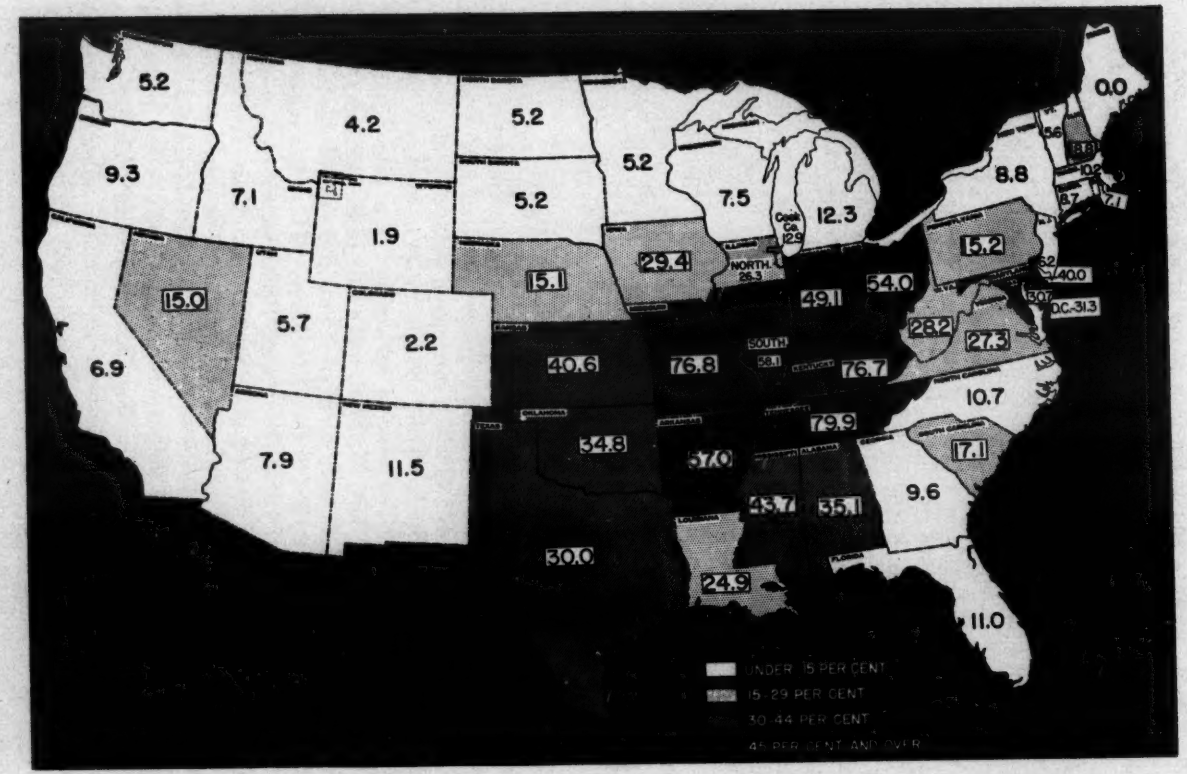

FIG. 1. The prevalence of histoplasmin sensitivity in per cent in residents of the United States, by states.

The Present Status and Clinical Interpretation of the Histoplasmin Test

Histoplasmin sensitivity is only a state of hypersensitivity induced by an experience with the fungus. As in the tuberculin test, the test qualitatively and quantitatively is no reflection of the state of activity of the infection with *H. capsulatum*. Conversion, or the development of sensitivity in the very young, probably signifies active disease. Sensitivity appears in from four to six weeks after infection begins, and may persist for many years after the infection has been healed, although there is evidence that anergy or loss of sensitivity occurs much more frequently than with tuberculosis. Massive progressive infection may suppress the humoral antibody titers and, with it, skin sensitivity is suppressed. It may even cause it to disappear entirely, since 50% of our cases of disseminated progressive disease do not have a positive skin test. Cross-sensitivity with the antigen complexes of other fungi has been demonstrated, but this fact is of little practical value or significance in the interpretation of histoplasmin sensitivity in suspected cases.

Clinical Manifestations

We have come to think of this disease in many ways as we think of tuberculosis. The parasitization by the yeast cell produces granulomatous lesions throughout the reticuloendothelial system. Pathologically there are many striking similarities between histoplasmosis and tuberculosis. Giant cell formations and caseous necrosis are present. There is likely to be a generalized reticuloendotheliosis, with blood stream dissemination to any or all organs. This being true, roentgenographically the lesions are frequently indistinguishable from the various forms of tuberculosis. The clinician will find it easy to think of the progressive disseminated variety of histoplasmosis as he would think of miliary tuberculosis or coccidioidal granuloma. In the same manner, he will see similarity between pulmonary histoplasmosis and the reinfection types of tuberculosis.

At the other end of this interesting disease spectrum, the healed primary lesions of histoplasmosis are comparable to those of acid-fast infections. Likewise, many clinical similarities will be found in intermediate forms of both diseases. The interpretation of the histoplasmin as well as tuberculin skin testing follows the same pattern.

The progressive forms of the disease are found very commonly in debilitated older persons who are rundown from chronic disease. It also seems to be more common in the very young, immunologically immature; at least 30% of the reported cases have occurred in those under 10 years of age. In this younger group the incidence is equal in both sexes; later, the male predominates, in a ratio of at least 3:1. No occupational predisposition has been noted, although it seems to be a rural disease.

Progressive Disseminated Histoplasmosis: In older individuals, about 50% of the cases present themselves with cutaneous or mucocutaneous lesions. These can be grouped as (1) ulcerations and granulomatous involvement of the naso-oropharynx; (2) purpuric manifestations, which are the ones more commonly found in childhood, and are associated with a generalized reticuloendothelioid reaction of the disease, and a crowding out of the normal bone marrow elements. This manifestation is a late and a bad prognostic sign; (3) nodules, papules, and punched-out, chancre-like ulcers, as well as abscesses and furunculoid pyoderma and impetiginous lesions.

In children, the progressive form of this disease is generally seen only after it has reached the moderately advanced stage, and at this time it is more apt to be considered by experienced clinicians to simulate aleukemic leukemia. A child might have been ill for one or two months with sickness and with increased irritability and fever. A number of the cases at the outset have recurrent or resistant diarrhea, occasionally with blood-tinged stools. There will be a weight loss or a failure to gain weight, and the child will become progressively paler until the family is likely to note enlargement of the abdomen. This is due to marked enlargement of the liver, and particularly of the spleen. The child will be irritable, apathetic and quite pale. The temperature is irregular, with daily elevations to 101 to 103° F. As a rule, there is no enlargement of the peripheral lymph nodes unless this adenopathy is regional and secondary to an ulcerative lesion. The absence of purpuric manifestations at this stage serves to differentiate it from acute leukemia, where the adenopathy is likely to be generalized and purpura prominent. Atypical pneumonia and pneumonitis and other pulmonary infiltrations, occasionally with thin-walled cavitation, are frequently present, as are ulcerative colitis and mesenteric adenitis. Still another group of cases, besides those simulating leukemia, are rather typical examples of Addison's disease.

We have recently seen a case whose signs and symptoms were indistinguishable from tuberculous meningitis. We were able to grow *H. capsulatum* from the spinal fluid. No acid-fast organisms were ever found. Pleocytosis, increased protein and decreased sugar in the spinal fluid were present. A tuberculin test was negative, but histoplasmin skin and complement fixation tests were 4 plus. Here is another part of this interesting disease spectrum which simulates tuberculosis. The central nervous system lesions have been beautifully described by Shapiro, Lux and Sprofkin in our clinic.[13]

With some exceptions, to be referred to later, clinically recognizable generalized disseminated histoplasmosis is uniformly progressive and fatal.

Benign or Nonprogressive Histoplasmosis: Up to this time we have described only the progressive, disseminated form of the disease, but the demonstration of the high prevalence of histoplasmin sensitivity in some parts of the world indicates that a number of individuals who are sensitive

to this skin test material must have become infected at one time or another, although they are entirely asymptomatic and have recovered spontaneously. These we refer to as asymptomatic benign infections, which acquire only histoplasmin sensitivity. In this form the fungus can rarely be recovered from blood or bone marrow, but histoplasmin conversion and humoral antibodies have been demonstrated to be present.

There is still another group of cases (which we call symptomatic benign) in which the disease is manifested by splenomegaly, or ulceration of the oropharynx with regional adenopathy or pulmonary infiltrations. These cases might also be called mucocutaneous manifestations of the disease. Though these are symptomatic, they are nonfatal and nonprogressive infections, and organisms can be found in the lesions by biopsy or by cultural method. However, they usually remain local in nature and do not disseminate.

It therefore seems that, because of this interesting generalized granulomatous reaction of the reticuloendothelial system, the virulence of the organism, resistance of the host and other unknown factors not only account for the protean nature of the clinical picture and the unusually interesting disease spectrum, but are also important in determining whether the disease remains local or becomes disseminated.

Finally, a considerable number of individuals in endemic areas must acquire histoplasmin sensitivity by an entirely asymptomatic means. These cases may or may not go on to pulmonary calcification, but histoplasmin sensitivity is always produced. Therefore, in the establishment of an early and accurate diagnosis of such a disease as histoplasmosis, with its variable clinical manifestations, the appropriate use of laboratory methods is essential. The need for histoplasmin tests, properly interpreted, and microbiologic technics for the demonstration of *H. capsulatum,* has been adequately established. It is hardly within the scope of this lecture to consider these laboratory methods—they have been adequately recorded and published elsewhere—but it is of practical importance to mention that, if we wish to grow the organism readily from contaminated material, blood or bone marrow, the media must be fortified by the addition of plasma or serum, and penicillin and streptomycin must be added to the media in appropriate amounts. At first we thought that the reason for this was to inhibit the pyogenic contaminants, but it would seem now that these additions enhance the growth properties of the media for the fungus. This is true in vitro. The use of these antibiotics in vivo in treating signs and symptoms which may be due to histoplasmosis would seem to be contraindicated.

In addition to the skin test and the cultural identification of *H. capsulatum,* for many years a number of serologic tests for histoplasmosis have been used by different workers. In our hands the complement fixation test has been most widely employed, and this can be valuable in following the course of a Histoplasma infection. In general, it may be said that complement-fixing antibodies are produced in most cases. This is an acute-phase

reaction, and the antibodies fade out after a period of a few weeks or months as the infection becomes asymptomatic or inactive. Properly interpreted, therefore, the test becomes of diagnostic as well as prognostic significance. At the present time our test is a complement fixation test, using both a yeast cell antigen and a mycelial antigen. Of the last 237 histoplasmin complement fixation tests that we have done, 31 have been positive with the yeast antigen and 71 positive with the mycelial antigen. Of these, 16 were positive with both antigens. There is a high correlation between positive tests and clinical disease. The tests in our hands are repeatable, and quite sensitive and specific. There is a placental transmission of histoplasmin complement-fixing antibodies from mother to infant, such as one sees in syphilis. This has recently been demonstrated by Zeidberg [14] at Vanderbilt.

Treatment

If one should wish deliberately to disseminate a primary infection which would of itself be self-limited, one should prescribe steroids. If one wishes to grow *H. capsulatum* from tissue body fluids or biopsy material, no matter how contaminated with pyogenic organisms, one should add antibiotics to the media. It is therefore likely that these are contraindicated in treating primary or even suspected histoplasmosis.

An effective treatment has not been found, however, and many drugs and antibodies have been tried by us and others without uniformly favorable results. Amphotericin B has appeared on the horizon, and some favorable results have been reported. In its present form, though, it is quite pyogenic, producing high fever and chills; it is poorly absorbed from the gastrointestinal tract, and renal toxicity has been observed.

I would like now to summarize our own most recent experience with one of the older therapeutic agents. Our attention was first called to the sulfonamides for the treatment of histoplasmosis by Curtis and Grekin in 1947.[15] These investigators were able to treat successfully with sulfadiazine two local mucocutaneous lesions which were proved to be due to Histoplasma. We attempted this therapy at that time on our disseminated, progressive types, but gave it up when the results were not immediately satisfactory and when we were able to show no in vitro effect against the organism.

A paper by Mayer and colleagues [16] in March, 1956, stimulated again our interest in the use of the sulfonamides as a therapeutic agent in histoplasmosis. These observers confirmed the low in vitro activity of the sulfonamides against *H. capsulatum,* but by the administration of sulfonamides mixed in the diet of mice infected with lethal doses of *H. capsulatum* they showed that this method was highly effective in giving greatly improved survival rates.

TABLE 1

Histoplasmosis—Treatment with Sulfonamides

Case	Race	Age	Sex	Duration	Signs and Symptoms	Diagnosis by				Rx Started	Rx Ended	Sulfa Levels mg.%	Present Status
						Biopsy	Blood Culture	Bone Marrow					
								Smear	Culture				
1 W. N.	W	3½ mos.	M	4 wks.	Cold "Almost pneumonia" Fever 103° Anemia Hepatosplenomegaly		+		+	9-27-56	11-6-56	14–25	Well
2 Q. K.	W	5 mos.	M	6 wks.	Malaise Fever Irritability Enlarged abdomen Hepatosplenomegaly			+	+	2-8-55	3-4-55	12–18	Well
3 L. T.	W	5 mos.	F	4 wks.	Cold Fever Spleen++++ Liver +++			+	+	11-14-56	11-21-56	10–21	Well
4 H. J.	W	72 yrs.	M	4 wks.	Ulcer tongue 2 × 2 cm. Weight loss 25 lbs.	+				9-11-56	2-11-57	Gantrisin 6 grams/d levels?	Well, wt. gain 20 lbs.
5 C. C.	W	40 yrs.	F	1 yr.	Sore tongue Hoarseness Dysphagia, laryngitis Ulceration hypopharynx Regional lymph nodes Weight loss—15 lbs.	+		+	+	7-17-54	8-15-54	9–13	Well

At this date we have treated five cases of histoplasmosis with sulfonamides. The first three of these, which appear in table 1, are of the progressive, disseminated variety. We have reason to believe these would certainly have been fatal. They were all culturally proved. The objective was to give triple sulfa suspension in doses which would produce levels in plasma of 12 to 15 mg. %. We were gratified, not by a prompt response, but after a matter of from seven to 14 days the temperature, which previously had been swinging to high levels, resolved and the children began to eat better and to gain weight. Eventually their splenic enlargement disappeared, their livers became smaller, and in approximately three to four weeks the children were well, and have remained well to this date. Two other cases which appear on the chart must be separated. These are older individuals, who presented themselves with the ulceroglandular type of proved but localized histoplasmosis. These individuals were like Curtis' cases, and there is possible precedent for these to be self-limiting, or at least to get well under a variety of different therapeutic agents. Under sulfonamide therapy they healed their lesions and regained their weight, and have been well for over a year. No recurrences have been noted, nor should they be expected. Certainly this method is easy to handle, methods for quantitating the therapeutic agent in the blood are well established, and the drugs are well tolerated. It is not clear at this time how the sulfonamides work on *H. capsulatum*. As a matter of fact, the same could be said for pyogenic bacteria, but this is certainly our method of choice in treatment at Vanderbilt at this time. We know of a number of other cases, from correspondence and telephone consultation, that also have gotten well. Several wide-scale evaluations are under way now in tuberculosis sanitoriums where sputum examinations can be carried out under sulfonamide therapy and with other agents, such as amphotericin B.

Summary

Since the introduction in 1945 of the histoplasmin skin test as a case-finding tool and as a means of establishing an epidemiologic index, human histoplasmosis has emerged from the category of a rare and esoteric disease to one which must be considered in any case where hepatosplenomegaly, fever, ulceration of the skin and mucous membranes and pulmonary lesions are otherwise unexplained. Prior to 1945, histoplasmosis was considered to be a uniformly fatal disease. It has now been established that there are many benign but symptomatic cases, and these are frequently recognized when one's index of suspicion is high and currently available laboratory aids are used. The geographic distribution is also much wider than was previously recognized.

This paper has briefly reviewed the accumulated knowledge of human histoplasmosis. Historical notes are presented on the problem of pulmonary calcification in nonreactors to tuberculin which led to the use of histo-

plasmin as a skin test material, and the relationship of sensitivity to pulmonary calcification has been briefly reviewed. The epidemiology of histoplasmosis and the clinical interpretation of the histoplasmin skin test are briefly discussed.

These studies have led to the description of benign forms of the disease with healing by calcification indistinguishable quite from tuberculosis. Asymptomatic and symptomatic but benign forms have also been described. The disseminated, progressive variety, with hematogenous spread to all organs or tissues of the body, completes the spectrum. All of these varieties remind one pathologically and roentgenographically of tuberculosis. Primary lesions have been demonstrated, as well as cavitary forms.

Current experiences with therapeutic agents have been presented. While the sulfonamides have little in vitro effect, they seem to offer some hope in the treatment of human disease.

Acknowledgments

For the privilege of being here this afternoon and being able to participate in the activities of this occasion, please accept this expression of my sincere appreciation. It is for me a great honor to be invited to address you and to receive your Award. It is, believe me, the most significant event of my career. I feel a sense of pride in and loyalty to the great institution, Vanderbilt University, whose setting made it possible for me to do the work leading up to this honor. This pride and loyalty, I know, is shared by all Vanderbilt men and women in the audience, and to them, many associates, former students and residents, I wish to extend my heartfelt thanks, not only for your help but also for your good wishes. I wish to extend my thanks to Dr. Goodpasture. When I came to him with an idea he gave it and me his every encouragement. I could not stand here without acknowledging my great indebtedness to Dr. J. C. Peterson, my former associate, who gave me his microbiologic knowledge, his loyalty and energy, and to Dr. Charles Smith, my old friend of California days, who contributed more to this presentation than I would have time to indicate on this occasion.

I had no way of knowing Dr. John Phillips, but I have a feeling that he would be pleased with the action of this College in honoring the work on this subject. This distinguished member and officer of your College in his lifetime contributed much to our knowledge of chest diseases. Your invitation finds me humble to have my name included in the long list of predecessors who have been asked to give the John Phillips Memorial Lecture, and proud because the very nature of my title indicates that this distinguished Society recognizes a contribution from a member of a group which has truly grown up.

And now on behalf of all those who helped me—teachers, colleagues, associates, residents, interns and students, and research committees such as that headed by Dr. Esmond Long, of the National Tuberculosis Association, may I extend my thanks and sincere appreciation. On behalf of patients and parents and of children yet unborn who will be aided by the clarification of these concepts, it is a privilege, a pleasure and a real honor to have been asked to give the John Phillips Lecture for 1958.

Summario in Interlingua

Depost le introduction in 1945 del test cutanee a histoplasmina como instrumento de detection del casos e como medio pro le establimento de un indice epidemiologic, histoplasmosis human se ha distachate ab le categoria de morbos rar e esoteric e ha devenite un entitate que debe esser prendite in consideration in omne casos in que hepatosplenomegalia, febre, ulceration cutanee e muco-membranal, e pathologia pulmonar es alteremente inexplicabile. Ante 1945, histoplasmosis esseva considerate como uniformemente mortal. Intertanto, il ha essite demonstrate que il existe multe casos que es symptomatic e nonobstante benigne. Istos es recognoscite frequentemente quando le indice de suspicion es alte e quando on se servi del technicas labora-

torial que es currentemente disponibile. Etiam le distribution geographic del morbo es multo plus extense que lo que esseva previemente recognoscite.

Le presente articulo offere un breve revista del accumulate cognoscentias con respecto a histoplasmosis in humanos. Es presentate notas historic con respecto al problema del calcification pulmonar in subjectos non reagente a tuberculina, i.e. le problema que duceva al uso de histoplasmina como material de testation cutanee, e etiam le relation inter sensibilitate e calcification pulmonar es delineate brevemente. Le epidemiologia de histoplasmosis e le interpretation clinic del test cutanee a histoplasmina es discutite summarimente.

Iste studios ha ducite al description de formas benigne del morbo con resanation per calcification non distinguibile ab illo de tuberculosis pulmonar. Es etiam describite formas asymptomatic e formas symptomatic sed benigne del morbo. Le varietate disseminate e progressive —con diffusion hematogene in omne organos e histos del corpore—completa le spectro. Omne iste varietates rememora tuberculose, tanto ab le puncto de vista pathologic como etiam ab le puncto de vista roentgenologic. Ha essite demonstrate lesiones primari e etiam formas cavitari.

Es presentate le experientias currente con varie agentes therapeutic. Le sulfonamidos es pauco efficace in vitro, sed in le therapia del morbo human illos offere un certe spero.

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THE GENETIC ASPECTS OF CARDIOVASCULAR DISEASES *

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THERE is a clinical impression of long standing that heredity plays some role in the pathogenesis of all four major types of cardiovascular disease: atherosclerosis (including coronary artery disease), hypertension, susceptibility to rheumatic fever (and therefore to rheumatic heart disease), and congenital malformations of the cardiovascular system.

These are diseases of multifactorial causation. To point to a genetic factor in coronary artery disease does not deny the possible importance of diet, stress, cigarette smoking, etc. To point to a genetic factor in susceptibility to rheumatic fever does not deny the paramount importance of the streptococcus. If one demonstrates a hereditary influence in some cases of congenital malformation, the greater importance, in other cases, of factors operating in the intra-uterine environment is not excluded.

Study of genetic factors is important (1) because potentially it will permit recognition of genetic susceptibles, for more effective application of preventive measures, and (2) because from our understanding of the mechanism whereby the gene or genes operate in these disorders can come preventive or therapeutic measures for breaking the chain leading to disease.

Already, thorough and critical investigations of major cardiovascular disease have provided corroboration of the clinical impression of a genetic factor. They have demonstrated a "familial aggregation" for each of the forms, and a pattern of aggregation consistent with genetic rather than environmental determination. What we need is a further quantitation of the genetic influence and an elucidation of the mechanism of gene-action in these diseases. For example, in essential hypertension, what is it that the individual inherits that predisposes him to hypertension?

But genetic analysis in major cardiovascular disease is extraordinarily complex and difficult. Partly for that reason I have chosen to confine the remainder of my remarks to an analysis of a much less common but genetically simpler form of cardiovascular disease, namely, that which occurs as an integral part of the Marfan syndrome.

THE CARDIOVASCULAR ASPECTS OF THE MARFAN SYNDROME

The victim of the Marfan syndrome is likely to show abnormalities in three areas:[1,2] in the eye, especially ectopia lentis (subluxation of the

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lenses); in the skeletal system, especially excessive length of the extremities; and in the cardiovascular system, especially a defect of the aorta media, which leads to diffuse aneurysm, dissecting aneurysm, or a combination of the two abnormalities (figure 1).

The aortic abnormality behaves like an abiotrophy, an inborn weakness which manifests itself only after a passage of time in the extra-uterine environment. Clinically evident aortic involvement may develop as early as the age of two years (figure 2) or as late as the forties. It is the very base

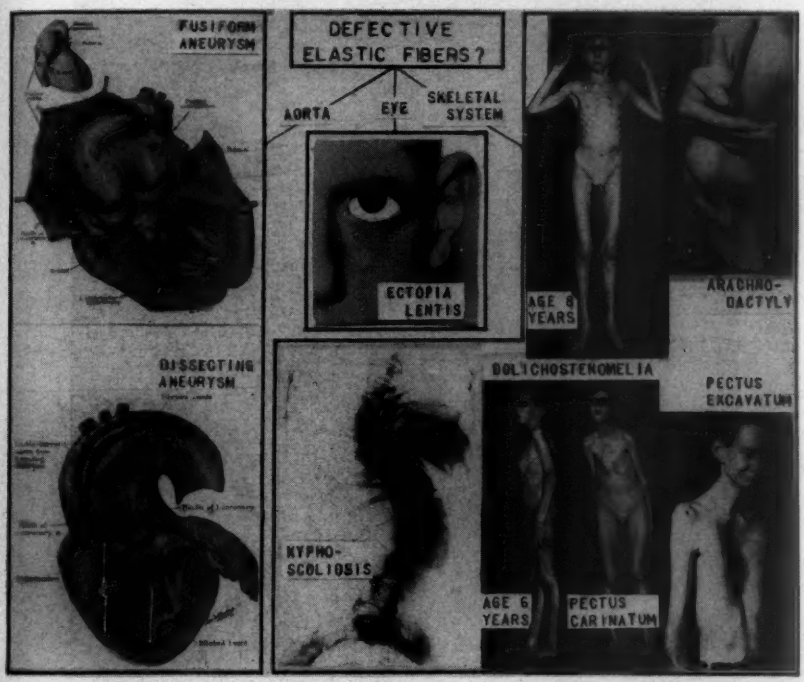


FIG. 1. A pictorial "pedigree of causes" relating the manifold manifestations of the Marfan syndrome to a postulated defect of the elastic fiber.

of the aorta, in the region of the sinuses of Valsalva, which undergoes dilatation first. Considerable aortic regurgitation may develop before there is evidence of aortic involvement by standard radiographic methods short of aortography.

It is the ascending aorta which is primarily involved in both processes, diffuse dilatation and dissecting aneurysm (figure 3). (The case presented in figure 4 represents a most unusual exception to the rule.) Although the gene-determined defect probably extends throughout the aorta, particular hemodynamic stress, specifically large expansile pulsations with each heart

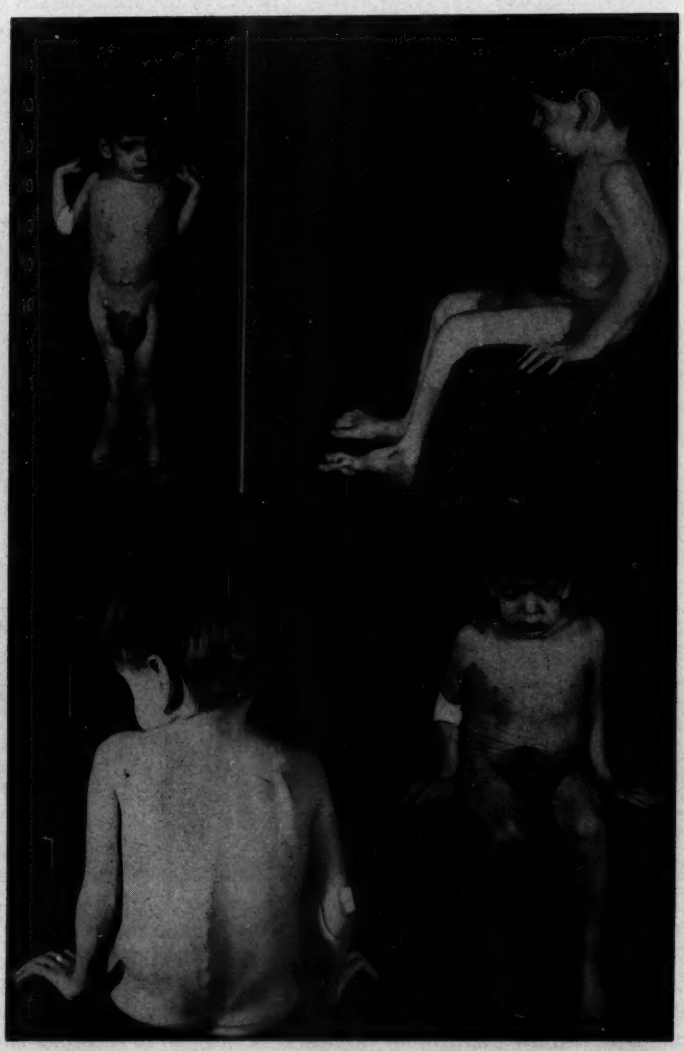
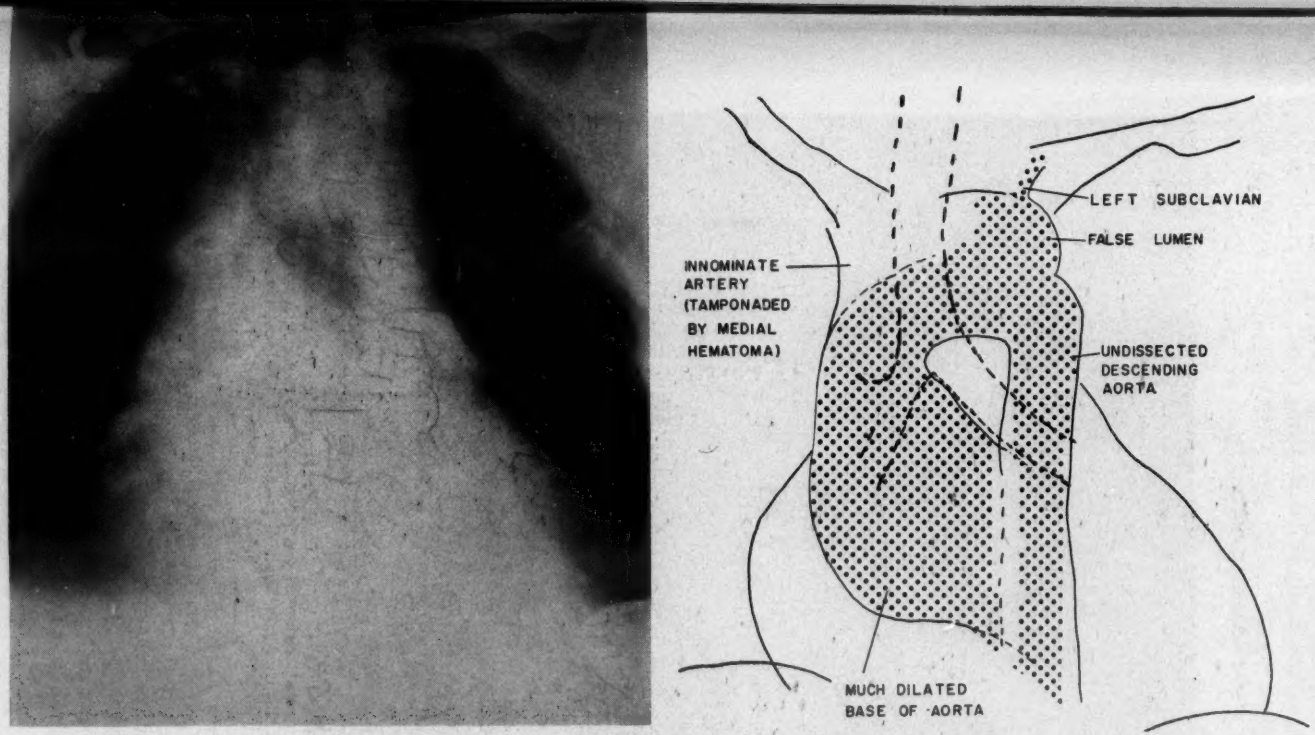


FIG. 2. J. M. G. (795394), age 26 months, has full-blown aortic regurgitation. The family history is negative. Dislocation of both lenses with striking iridodonesis, characteristically misshapen head and ears, kyphoscoliosis with "cat-back" in sitting, arachnodactyly, a large left inguinal hernia are present.



A B

FIG. 3 A and B. S. C. (575946), a veterinarian, had ectopia lentis and skeletal proportions of the Marfan syndrome. He died at the age of 37 years during an attempt at surgical repair of the ascending aorta. With the episode of dissection in October, 1955, a musical systolic murmur developed over the ascending aorta. This sign, a valuable diagnostic clue in such cases, probably owes its origin to vibration in intimal lip or fibrous bands in the ascending aorta. Angiocardiogram (A and B) showed striking dilatation of the base of the aorta within the shadow of the heart, surprisingly little enlargement of the later portion of the ascending aorta, failure of opacification of the innominate artery the lumen of which was tamponaded by a medial dissection, and, finally, pseudocoarctation of the type so typical of the Marfan syndrome.

beat, occurs predominantly in the ascending aorta. The combination of this local stress with the generalized connective tissue defect probably determines localization in the ascending aorta.

FIG. 3 *continued.* C. The gourdlike appearance of the ascending aorta as exposed through a surgical incision in the right anterior thorax. A clamp lies under the right coronary artery. Unusually high displacement of this vessel made operation difficult, as did also the high extension of the aortic commissures. The patient died during surgery. The aortic findings at autopsy were strikingly similar to those shown in the lower left of figure 1. The mother of this patient died of the cardiac complications of the Marfan syndrome at the age of 40 years. An older sister of the patient has the Marfan syndrome.

The clinical behavior of dissecting aneurysm in the Marfan syndrome is not different from that described for dissecting aneurysm in general, except, of course, that the patient is usually younger, and aortic regurgitation is much more likely to be present, whereas hypertension is usually absent.

Idiopathic cystic medial necrosis, which also involves predominantly the ascending aorta and has to an increasing extent been recognized clinically in recent years,[3] probably involves the sinuses of Valsalva less extensively than does the Marfan syndrome.[4] For this reason surgical attack is more feasible than it is in the Marfan syndrome (figure 3).

The pulmonary artery may be involved in a manner similar to the aortic involvement.

FIG. 3 *continued.* D. The proband's sons, one affected (left), one unaffected, are seen here. R. C. (783343), the affected boy, eight and three quarters years old, has grossly visible dislocation of the lenses, myopia, mild thoracic kyphosis. The normal brother is 12 years old; another brother, age four years, is also normal.

Atrial septal defect occurs much less commonly than was previously thought. The single case in my own series that I thought had this malformation (figure 18, page 60, reference 2) was found to have an intact atrial septum at necropsy.

Pectus excavatum occurs commonly in the Marfan syndrome. (Some type of chest deformity occurs in the majority of cases.) Probably only a small percentage of all cases of pectus excavatum are instances of Marfan's syndrome. However, in evaluating cardiac symptoms with pectus excavatum, one must keep the Marfan syndrome in mind. If there is an aortic

diastolic murmur, the likelihood of the Marfan syndrome is especially great. If the heart is normal by usual tests, surgical correction of the pectus excavatum in the Marfan syndrome is feasible. Healing proceeds normally. Surgery should be postponed until after full growth is attained.

FIG. 4 A. E. K. (760410), age 26 years, was admitted for consideration of surgical correction of an abdominal aneurysm. The skeleton was considered to be typical of the Marfan syndrome. Both lenses were displaced upward and outward. The patient was partially deaf, but this was of the conductive type, was largely limited to the left ear, and was readily accounted for on the basis of old otitis media.

The Marfan syndrome is inherited as an autosomal (nonsex-linked) dominant (figure 5). Although facsimiles of the genuine condition occur, there is, as far as is known, only one genetic variety of the disease. It seems

to arise by *de novo* mutation fairly often, so that "sporadic cases" are observed.

Not only does the occurrence of skeletal features at least vaguely suggesting the Marfan syndrome, together with a variety of congenital cardiac malformations, introduce diagnostic confusion—the exceedingly wide range of

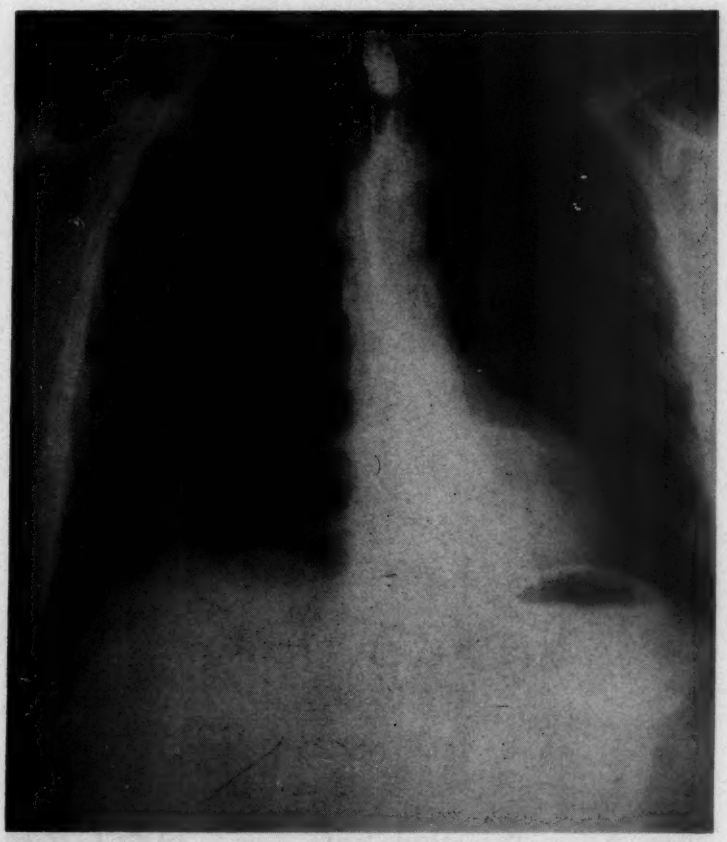


FIG. 4 *continued.* B. There was no aortic regurgitation. The thoracic aorta seems normal radiologically down to a point just above the diaphragm, where it became abruptly larger.

severity of involvement in cases of Marfan's syndrome and the variability in relative strength of the several components are also bases for diagnostic puzzlement. It is a generalization in medical genetics that "dominant traits" display greater variability than do "recessive traits." Such is the case in the Marfan syndrome.

The skeletal aspects of the Marfan syndrome may be simulated by certain pathologic states, such as eunuchism (prepuberal castration) and sickle cell anemia. The skeletal proportions in some ethnic groups also represent a phenocopy (figure 6).

Especially in the Negro, but in others as well, the question of whether the Marfan syndrome is present comes up frequently. Is an otherwise un-

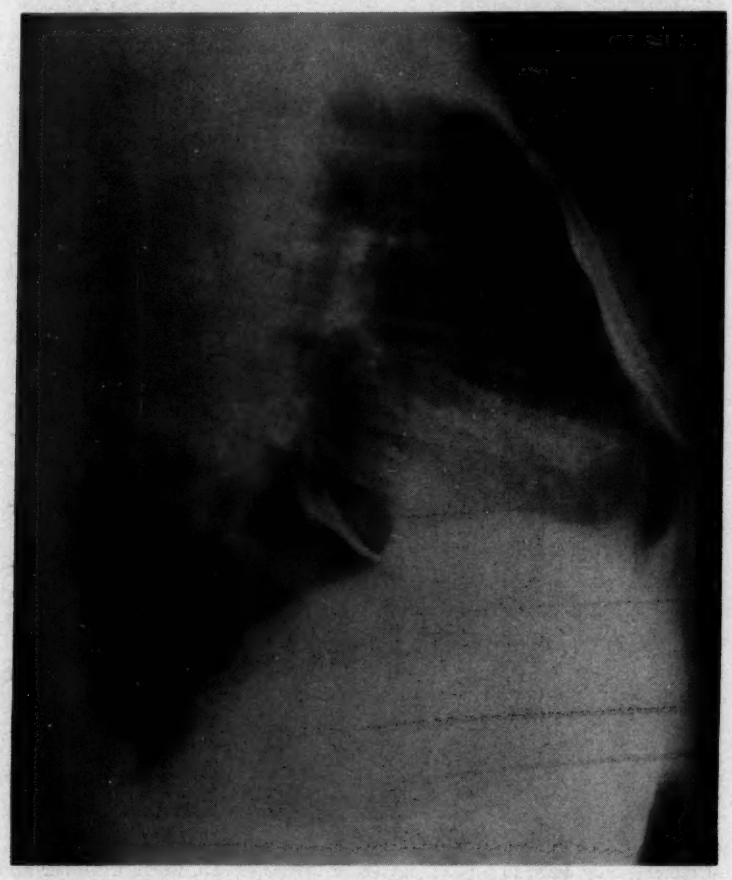


FIG. 4 *continued.* C. The deformity of the sternum is evident.

explained aortic regurgitation or aortic aneurysm on this basis? In such questionable cases one should (1) examine the patient's eyes under the slit lamp with full mydriasis for evidences of even slight displacement of the lenses, and (2) investigate the family for history of unusual habitus, eye trouble, hernia, or heart trouble in young persons.

If both of these investigations are negative, one can arrive at no definite conclusion as to whether the Marfan syndrome exists or not. It is certain that the rest of Marfan's syndrome can occur without ectopia lentis.

Is there a single basic biochemical defect for which the mutant gene is responsible and which in turn is responsible for the diverse manifestations

FIG. 4 *continued.* D. The enlargement of the aorta was shown by aortography to be cylindric and to extend the full length of the abdomen. The aneurysm was easily felt and seen on abdominal examination.

of the Marfan syndrome? Because of the changes observed in the aorta, the elastic fiber or some connective tissue element intimately associated with it comes under immediate suspicion. If we knew what the suspensory liga-

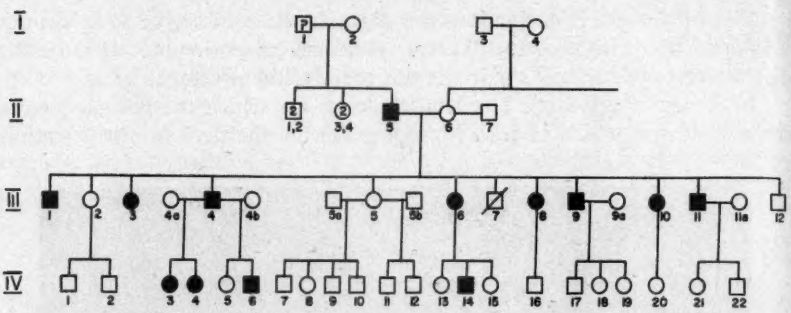


FIG. 5. The Marfan syndrome in three and probably four and more generations. I 1. Died at 39 years after brief illness. II 1. John Peter S., died at age 50 years of dissecting aneurysm of aorta. Had bad eyes. III 1. John A. S., born September 29, 1913. Has ectopia lentis and severe myopia. Strabismus. 2. Elizabeth S. M., born 1915. Unaffected. Requires hearing aid. 3. Hilda S. S., born 1918. Ectopia lentis, severe myopia, chest deformity, dolichostenomelia. 4. Joseph William ("Jodie") S., born 1921. Ectopia lentis, left myopia, dolichostenomelia. 5. Frances S. Z. O., born May 9, 1922. Small left posterior pole cataract. One of her six children is deaf. Probably unaffected. 6. Naomi S. M., born Jan. 27, 1924. Ectopia lentis, severe myopia, "tongue-tied," with indistinct speech. 7. Died at one year of "summer complaint." 8. Mildred S. D., born July 10, 1928. Ectopia lentis and severe myopia. 9. Frank Martin S., born April 9, 1931. Ectopia lentis, severe myopia, dolichostenomelia, severe pneumonia twice as child, slight sternal depression and left chest deformity, hernia. 10. Nancy Patricia S. M., born 1932. Ectopia lentis and myopia. 11. Walter Raymond S., born February 5, 1934. Ectopia lentis, myopia, dolichostenomelia, history of severe pneumonia, chest deformity. 12. Jerome S., born 1935. Unaffected apparently, but had operation for severe strabismus in 1949. IV 3. Katherine S. Affected. 4. Mary Dorothy Diane S., born December 19, 1943. Bilateral immature cataract and ectopia lentis. Affected. 6. Probably affected. 14. Harry Douglas M. Jr., born 1945. Trouble talking like mother. Chicken breast, myopia. 15. Sophronia M., born 1947. Apparently unaffected. Trouble talking distinctly. (In a family of 12 children—see generation III—the chance of 8 or more children being affected is almost one in four.)

ment of the lens and the media of the aorta have in common, the nature of the basic defect might be more evident. How can one account for the excessive longitudinal growth of round bones on the basis of an elastic fiber defect? One possibility is that a defect in the connective tissue of periosteum (which normally exercises some control over longitudinal growth because of its attachment to the epiphyses) results in loss of restriction on longitudinal growth.

SUMMARIO IN INTERLINGUA

Il pare que le hereditate ha un certe rolo in omne le quatro typos principal de morbo cardiovascular: Atherosclerosis, hypertension, febre rheumatic, e malformation congenite.

Le plus grande parte del presente articulo es concernite con un discussion del aspectos cardiovascular del syndrome de Marfan. Le multiple componentes de iste syndrome es presentate. Le aorta ascendente es implicate primarimente, per dilatation diffuse o per aneurysmo dissecante o per ambes. Tamen, in casos rar il occurre que le aorta abdominal es implicate primarimente. Il pare que le syndrome de Marfan depende de un sol gen mutante que se comporta como dominante autosomal. Le natura del basic defecto de histo conjunctive es non ancora cognoscite. Tamen, le fibra elastic—o un elemento intimemente associate con illo—se trova sub suspicion.

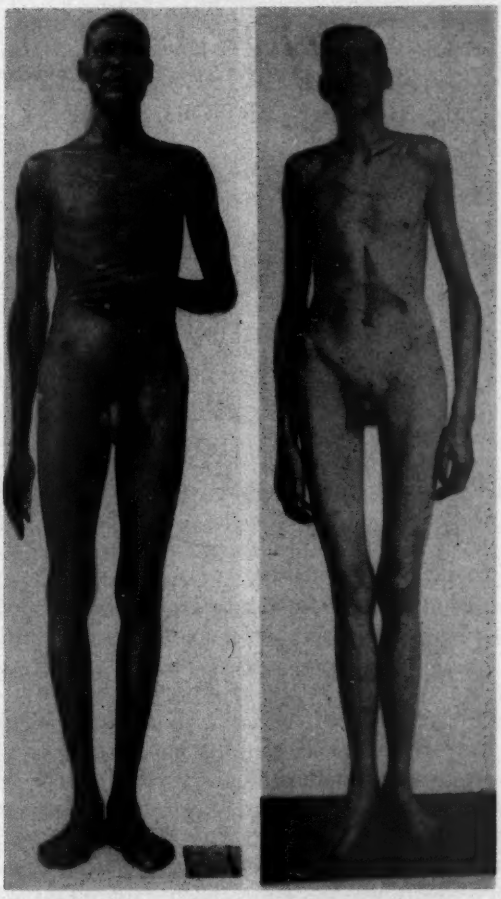


FIG. 6. Phenocopies of the Marfan syndrome. The Denker Negro, left; eunuch, right.

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BRUCELLOSIS AND HEART DISEASE. III. CHRONIC VALVULAR HEART DISEASE FOLLOWING NONFATAL BRUCELLOSIS *†

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IN an earlier study [1] in this series it was noted that endocarditis is the most frequent cause of death in fatal brucellosis. Do valvular lesions also occur in nonfatal brucellosis? We have sought an answer to this question by reviewing the literature on nonfatal brucellosis, and by studying patients in whom heart disease and brucellosis have been associated.

HISTORICAL EVIDENCE OF CARDIAC INVOLVEMENT IN NONFATAL BRUCELLOSIS

Early writers had much to say about involvement of the cardiovascular system in brucellosis. Veale,[2] one of the first to write on what was almost certainly brucellosis, described the case of a 24 year old soldier who contracted the fever in Gibraltar in 1879. During the course of his illness, murmurs appeared at the mitral and aortic areas, and gradually disappeared with recovery. Hughes,[3] in his classic monograph published in 1897, noted that "cardiac valvular disease is a most serious complication, though not necessarily fatal. . . . " Bassett-Smith [4] wrote in 1906 that " . . . at the present time hardly enough value has been given, for diagnosis, prognosis or treatment, to the important effects produced by the specific organism of Mediterranean fever on the heart." He stated that he knew of 42 cases that were invalided out of military service following the infection, and of these, "eleven were for organic heart disease, due to, or occurring with the fever." He also knew of additional cases where heart murmurs developed but where the disability was not sufficient to require that they be invalided. Attinger [5] reported two cases where serious cardiac manifestations developed during brucellosis. One of these, a 57 year old farmer who had had a normal heart on prior examination, developed constricting precordial pain, enlargement of the heart and total irregularity of the rhythm during the course of his fever. No murmurs were noted. The symptoms and signs continued long into convalescence, but the patient eventually recovered. Attinger's other case was a young farmer who developed irregular pulse,

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systolic aortic murmur and cardiac enlargement following undulant fever; this patient also recovered. Raynaud [6] and his co-workers in France wrote of two patients with previously normal hearts in whom aortic murmurs appeared during brucellosis and persisted, along with dyspnea on exertion, after all signs of infection had gone. These authors noted that embolism was rarer in brucellar endocarditis than in other forms of infectious endocarditis. Rubegni [7] noted the occurrence of valvular heart disease during brucellosis, and implied that it was not always fatal. He quoted a case published by Liverani (which we have not been able to find in the original) where recovery followed a six-month illness manifest by fever, weakness, abdominal pain, purpuric hemorrhages, and a soft diastolic aortic murmur. Stigliani [8] referred to two patients who developed systolic murmurs during the course of brucellosis and who later recovered.

(It should be noted that in each of the cases of endocarditis referred to above, and also in each of the new cases reported herewith, recovery was spontaneous rather than a result of modern chemotherapy. Thus healing is shown as a part of the natural history of the valvular lesion, a thing which was suggested by the pathologic findings in fatal cases of brucellar endocarditis.[1])

Recent American studies on brucellosis have dealt chiefly with the effects of therapy. Among these are a number of instances of endocarditis with recovery. Quinn and Brown [9] reported the case of a 25 year old male with aortic and mitral endocarditis and with blood cultures positive for both *Brucella abortus* and *Streptococcus viridans.* Under antibiotic therapy he recovered but signs of valvular disease persisted. Hudson [10] has recently described a case of *Br. abortus* endocarditis of the aortic valve where recovery occurred on antibiotic therapy.

Spink,[11] in his recent book, *The Nature of Brucellosis,* gives brief summaries on 244 cases of brucellosis studied at the University of Minnesota Hospital between 1937 and 1954. Three patients died of their infection; all of these (cases 1, 4 and 29) were instances of *Br. abortus* endocarditis involving the aortic valve. Three other patients died at home during the period of observation, but apparently not of brucellosis: case 23 of cirrhosis of the liver after a period during which bundle branch block was noted; case 25 following an accident, and case 55 of hypertension and cerebral hemorrhage. Among the cases that survived, cardiovascular abnormalities were recorded as follows: subacute bacterial endocarditis of the aortic valve, one (case 33); aortic stenosis, two (cases 10 and 174); "systolic and diastolic aortic murmurs," two (cases 78 and 241); bundle branch block, one (case 95); hypertensive heart disease, one (case 185); and "arteriosclerotic heart disease," one (case 6). In addition, eight patients (cases 19, 31, 41, 43, 47, 62, 66 and 117) were noted to have systolic murmurs at the apex, and two patients (cases 7 and 96) were said to have a history of rheumatic fever; the brief summaries do not reveal whether organic heart disease was present in these 10 patients. (Spink assigns the cases of subacute bacterial

endocarditis to the Brucella infection, but implies that in all the other cases the heart disease was unrelated.)

Several European and South American investigators have studied the frequency of cardiac involvement in brucellosis. Posteli, Altana and Rosa [12] noted some degree of involvement of the cardiovascular apparatus in 53 of 75 cases of brucellosis studied clinically. The finding most frequently recorded was hypotension; in eight cases, heart murmurs associated with cardiac enlargement were noted. Signs of myocardial involvement were detected in two other cases.

Moeschlin [13] studied 34 patients by electrocardiography and found changes interpreted as "myocardial damage" in 11. Prolonged conduction time, inverted T waves in Lead 2, abnormal Q waves in Lead 3, abnormalities of rhythm, etc., were all observed. In some instances these changes were associated with heart murmurs.

Amuchastegui [14] made careful cardiovascular studies in 116 patients with brucellosis. The group included 61 adults and 55 children. Among the adults, signs of valvular lesions were noted in 27 cases; most of these were interpreted as mitral insufficiency. Evidence of myocardial disease was detected electrocardiographically in 38 of the adults; the usual changes were notching and slurring of complexes. Among the 55 children, valvular murmurs were noted in 22 instances, the usual diagnosis being mitral insufficiency. Electrocardiographic evidence of myocardial disease was noted in 31 of the children. Using standard and precordial (C R 1–3 and 5) leads, and repeating the examinations at intervals, he found abnormalities at some time during the illness in 93.3% of the 116 cases. By studying these cases at intervals for from one to two years after recovery from the infection, Amuchastegui noted disappearance of the electrocardiographic abnormalities. From this he concluded that most of the changes recorded were due to brucellosis rather than to some concurrent disease.

Maldonado-Allende,[15] also writing from Argentina, reported on 428 cases of brucellosis seen during a 10-year period; apparently most of these cases were ambulatory. In 55 cases (12.8%) there was evidence of cardiovascular disease, but in only 47 cases (10.9%) was the cardiovascular involvement believed to be due to brucellosis. Included were a number of cases of arterial hypertension. Bundle branch block was noted in six cases.

Poli,[16] in an Italian-language monograph entitled "Cardiovascular lesions caused by Brucella," reported the results of an examination of hospital records dating back to 1908. He found 166 cases diagnosed as brucellosis; there were cardiac abnormalities in 56 instances, but often it was not possible to determine whether the abnormalities were due to brucellosis. Judged by modern standards these records were inadequate and inconclusive. Poli also examined the charts of 329 cardiac patients (type not stated) searching for evidence of prior brucellosis, but found none recorded.

Panuccio [17] studied 137 patients admitted to hospital because of brucellosis covering a 10-year period. In 22 of these cases there was evidence of

myocarditis due to brucellosis. In three other cases myocarditis was thought to be due to rheumatic infection.

In spite of the evidence in the literature that the heart may be affected in nonfatal brucellosis, we are not aware of any reports of chronic valvular heart disease following brucellosis. It has been generally held that almost all such cases are a result of either rheumatic fever or syphilis.

Report of Cases of Chronic Valvular Heart Disease Following Brucellosis

In each case reported here a clinical diagnosis of brucellosis has been made, usually elsewhere. In some the diagnosis of brucellosis was based on serologic data; in others the evidence is circumstantial; in no case was there a record of positive culture for Brucella. As is so often the case with both brucellosis and rheumatic fever, it is sometimes impossible to establish the diagnosis beyond a reasonable doubt.

The first four of these cases were discovered by investigating patients presenting as pure aortic valve disease, this being the specific lesion suggested by the autopsy findings in fatal brucellosis.[1] The remaining cases came to light by searching out patients with a history of brucellosis and studying them for evidence of residual cardiac disease. So that the sequence of events can be clearly shown, the details of each case are presented chronologically rather than in the order in which the facts became known to us.

Case Reports

Case 1. A widow from a small rural community in southwestern Virginia developed undulant fever at age 64 and was treated by Dr. Philip S. Smith, of Abingdon, Virginia. Dr. Smith furnished the following information in reply to a letter. The patient had been admitted to the Johnston Memorial Hospital in Abingdon on March 4, 1946, complaining of sore throat for from five to six weeks, and chills, weakness and fever for about two weeks. At times the temperature had been as high as 105° F. Before admission her Brucella agglutination had been tested twice, the first having been positive 1:40, the second positive 1:120. After admission the titer continued to rise, reaching 1:320. The temperature curve was, according to Dr. Smith, "typically undulating in type." The patient had severe sweats while in the hospital, acute joint pains, and the spleen was palpable. The heart was not enlarged, and there were no murmurs or arrhythmias. The x-ray of the chest showed nothing significant. The temperature was still elevated when she left the hospital on June 12, 1946, and, according to the patient, fever continued for several months thereafter.

In April, 1953, the patient was found to have a heart murmur, and soon thereafter was referred to Dr. John W. Du Chez, Clinical Instructor in Medicine, The George Washington University, for evaluation. Dr. Du Chez obtained the history of prior brucellosis and called the case to our attention. The following data are from his office record of the case.

In May, 1953, there was no evidence of cyanosis, venous distention or edema. The pulse rate was 84; temperature, normal; blood pressure, 132/74 mm. of Hg. There was no apparent cardiac enlargement. The heart sounds were of good quality. A grade 3 systolic murmur was heard over the entire precordium with the patient

supine; with the patient standing and leaning forward the murmur was maximal in the aortic area. The aortic second sound was relatively normal. The first mitral sound was snapping. On fluoroscopy the lung fields were clear, and there was no apparent cardiac enlargement. No calcium was observed in the valve areas, but Dr. Du Chez believed that calcific aortic stenosis was present. There was no evidence of functional impairment at this time. An electrocardiogram was within normal limits except for borderline evidence of low voltage in the limb leads. There were no cardiac symptoms in 1957, when the patient was seen again for a urinary complaint.

Case 2. This married woman had been perfectly well until 1930 when, at age 26, she spent several months on a farm in Iowa. During this period she drank raw milk brought warm from a nearby farm. Later in the summer she developed marked fatigue, fever, sore throat and occasionally a "deep cough." The fever was generally 99 to 100° F. and was intermittent. There were no joint symptoms or other pains. After returning to Washington in the fall of 1930 her symptoms persisted. On July 31, 1934, she was admitted to The Johns Hopkins Hospital complaining of recurring episodes of fever, pain over the heart and dyspnea. On examination the heart was slightly enlarged to the left and there was a very short, presystolic thrill. A systolic murmur and a short, late diastolic murmur were heard at the mitral area. The blood pressure was 115/78 mm. of Hg. Serum agglutination of Brucella organisms was positive 1:640, and this was confirmed by a second test. The patient was discharged on August 4, 1934, with a diagnosis of undulant fever. Gradually the intervals of fever and aching precordial pain became shorter and less severe, although they continued in all for some 10 to 12 years from the onset. Murmurs were inconstant, but a precordial systolic murmur, loudest at the aortic area, was usually noted. At no time preceding or during this long illness was there a suspicion of rheumatic fever.

On June 8, 1953, the patient was bitten by a dog and four days later was admitted to Circle Terrace Hospital in Alexandria, Virginia, under the care of Dr. Charles V. Amole, for the treatment of cellulitis of the arm. The murmurs of aortic valve disease and the history of brucellosis were recorded by Dr. Stephen Djeter, who kindly brought the case to our attention.

The patient was seen in consultation by Dr. Ben C. Jones, Clinical Instructor in Medicine, The George Washington University. For several years there had been shortness of breath on exertion, and occasional spells of palpitation and ankle edema. The apical impulse was in the sixth intercostal space 11 cm. from the midsternal line. A grade 3 systolic murmur was audible over the entire precordium but was loudest in the third interspace just to the left of the sternum. A diastolic murmur could also be heard in the same area. The aortic second sound was of poor quality. The blood pressure was 120/70 mm. of Hg. A chest x-ray showed no abnormality of the lungs; the cardiac contour was consistent with aortic stenosis. Calcification of the heart valves was not demonstrated. The electrocardiogram was within normal limits. The patient was discharged on June 19, 1953, in good condition.

Case 3. A 45 year old married woman was admitted to the George Washington University Medical Division of the District of Columbia General Hospital on January 18, 1953. She was disoriented and sometimes illogical in answering questions, but stated that her "heart had been acting up for over a month." Dyspnea, edema and cough had been noted for the same period of time, but there had been no hemoptysis or chest pain. On the night before admission she had fainted and had been unconscious for about 15 minutes. Because of the memory defect it was not possible to determine many details of the history. She denied having had rheumatic fever. She had spent her early years on a farm.

On admission the temperature was 103.2° F.; pulse, 120; respiration, 24; blood pressure, 100/80 mm. of Hg. The lungs showed moist râles bilaterally. The heart sounds were somewhat distant but the rhythm was regular. There was a harsh grade 3 systolic murmur, best heard at the aortic area, with transmission into the neck vessels and downward along the left border of the sternum. The second aortic sound was of reduced intensity. The liver was enlarged and tender. The spleen was not felt. There was 4 plus pitting edema of both legs. Chest x-ray showed generalized enlargement of the heart and irregular shadows in both lung fields. The patient was treated with oxygen, Digoxin and erythromycin, and improved rapidly.

On February 5, 1953, the patient's cardiac status was reviewed by one of us (J. M. E.). The murmur was essentially unchanged. A systolic thrill was demonstrated along the course of the right common carotid artery. Fluoroscopy revealed left ventricular enlargement and calcification of the leaflets of the aortic valve. The Brucella agglutination was positive in a dilution of 1:640. The patient remained under observation for several months. When last seen she was still free of fever. The cardiac findings and mental confusion persisted. The Brucella agglutinin titer had fallen to 1:20.

Case 4. This male patient had two prolonged periods of fever, each lasting about one year. The first occurred at age 15 and was manifest by intermittent pain and swelling of the joints. The second occurred several years later and was diagnosed as typhoid fever. From about age 35 to 42 he was frequently troubled with low back pain ("sciatic rheumatism"). He lived and worked on farms in North Dakota, Iowa and Minnesota from boyhood until age 44, except for a period of two years when he worked as a butcher. After age 44 he worked as a heating and air conditioning engineer. There were no symptoms of heart disease. From age 67 to 69 there were three periods of illness, each lasting several weeks, manifest by fever, sweats and pain in the joints (left shoulder, cervical spine, left foot). In 1948, at age 69, he was admitted to Sibley Memorial Hospital, Washington, D. C., under the care of Dr. John F. Finnegan. He had had chills, fever and joint pains for six weeks. At this time a rough systolic murmur was heard, loudest at the aortic area but heard well over the whole precordium and transmitted upward into the vessels of the neck. Several petechiae were noted in the skin of the abdomen. For two days after admission the temperature was generally about 101° F. This was followed by an afebrile period lasting several days. Then there was a second period of fever lasting four days. A blood culture was negative. The leukocyte count was 9,500. The tentative diagnosis of subacute bacterial endocarditis was changed to undulant fever in spite of a negative agglutination test with Brucella antigen.

Beginning three years later, at age 72, there were recurring episodes of dyspnea, substernal pain radiating down the left arm, and ankle edema, for which the patient was repeatedly admitted to the Arlington Hospital, Arlington, Virginia, under the care of Dr. K. N. Ostergard. On each admission the temperature was elevated (100 to 104° F.), and on several occasions there were drenching sweats and hot, swollen joints. Heart findings were essentially unchanged from those noted three years earlier. Blood cultures were repeatedly negative. The Brucella agglutination was positive 1:160; all other agglutination tests were negative. The electrocardiogram showed evidence of complete right bundle branch block. The patient died at age 76 during an episode of substernal distress, dyspnea and cyanosis. Dr. William Dolan, pathologist at Arlington Hospital, revealed the details of this case to us and permitted us to examine the various organs post mortem.

Autopsy Findings: At autopsy the significant changes were confined to the heart, which was both hypertrophied and dilated. The pericardial sac was obliterated by fibrous adhesions between the two layers. The structures of the right side of the heart were completely normal. The left atrium was slightly dilated but its endo-

cardium was smooth. The mitral valve showed no thickening of the cusps and no agglutination at the commissures. The chordae tendineae were not thickened or fused. There was slight calcification for about 0.5 cm. of the circumference of the mitral valve ring, but this caused no appreciable distortion of the orifice. In the myocardium of the left ventricle, near the apex and laterally, there was a fibrous scar 1 cm. in greatest diameter, equidistant from the endocardium and the epicardium. The aortic valve cusps were nodular and calcified. The right cusp and the posterior cusp were fused at their commissure. At the bottom of the right cusp there was a smooth round hole 0.2 cm. in diameter. The right-left commissure showed no nodularity or distortion. There was minimal atheromatous streaking of the intima of the coronary arteries, without appreciable narrowing of their lumina.

Microscopically the aortic valve cusps were greatly thickened and showed irregularly rounded masses of calcium embedded in dense hyaline connective tissue. (Photographs of the valvular lesion in this case are reproduced as figure 4 in the fourth paper in this series.[18]) Sections of myocardium showed a fibrous scar, presumably due to a small old infarct, but no active inflammatory lesions were noted.

Case 5. A veterinarian * who worked chiefly with hogs and cattle developed at age 22 a protracted febrile illness which, according to his mother, was diagnosed as brucellosis; the basis for the diagnosis is not known. Two years later he came under the care of Dr. J. C. Sherrick, now of Chicago. The patient gave a history of prior brucellosis but according to Dr. Sherrick showed no evidence of the infection. At this time there was evidence of slight cardiac enlargement. A low, rumbling, mid-diastolic murmur and a harsh systolic murmur were heard at the apex. The blood pressure was normal. Subsequently (at age 25) there was an episode of cerebral hemorrhage which left the left side paralyzed. Two years later there was a second cerebral hemorrhage which proved fatal. Dr. Sherrick removed the heart and brain and forwarded them to Dr. A. L. Sahs, of the Department of Neurology of the State University of Iowa. Dr. Sahs has kindly informed us that there was evidence of mitral stenosis, which he interpreted as being of rheumatic origin. The brain showed a berry aneurysm of the left anterior cerebral artery. The aneurysm had ruptured and the blood had dissected extensively in the left cerebral hemisphere, finally breaking into the left lateral ventricle. The aneurysm was considered to be of congenital origin.

Case 6. A veterinarian who worked chiefly with cattle and hogs, some of the former known to be affected by Bang's disease, developed a febrile illness in the summer of 1916, at the age of 32. With the help of a driver he was able to make calls during the summer and fall, but spent such time as he could in bed. His physician was convinced that he had "Malta fever," but there was no confirmation. With cold weather the fever gradually subsided. The patient was able to return to full activity in his profession, but there were occasional pains in the shoulders and hips, and some sweating at night until about age 46. There was no history of rheumatic fever, chorea or scarlet fever. He saw Army service in 1918, and had several examinations for insurance without heart disease being detected.

The patient was generally well until about age 54, when he had a sudden feeling of weakness, trembling, and "feeling sick." He was told at this time that he had heart trouble, and was advised to restrict his activities.

In May, 1945, at age 61, he had sudden, sharp precordial pain radiating to the left shoulder, lasting half an hour and relieved by nitroglycerin. A few days later he was admitted to the State of Wisconsin General Hospital, Madison, Wisconsin,

* This case and the one following were obtained from a study of causes of death in veterinarians.[19] This study was undertaken to find cases of severe brucellosis; the morbidity rate from brucellosis is higher in veterinarians than in any other occupational group.[20]

under the care of Dr. H. H. Shapiro, who kindly furnished us with the following information. On examination the pulse was of small volume and plateau-like; rate was 60 per minute. The blood pressure was 140/90 mm. of Hg. A very loud, harsh systolic murmur was heard at the aortic area and was transmitted along the great vessels. No diastolic murmur was heard. On fluoroscopic examination, calcification of the aortic valve was demonstrated; there was also left ventricular enlargement.

When next seen by Dr. Shapiro in April, 1946, the patient complained of fatigue, marked dyspnea on exertion, and aching substernal pain radiating down both arms. A faint systolic thrill was felt at the aortic area at this time, and the harsh systolic murmur was now described as "nozzle-like." There were subsequent out-patient visits in March, 1947, and in August, 1948; symptoms and findings were relatively unchanged.

In November, 1948, the patient came under the care of Dr. W. F. Kammer, of Muncie, Indiana, who has kindly given us additional information. The signs of calcific aortic stenosis persisted, on both physical examination and fluoroscopy, and there was evidence of severe myocardial failure. Death occurred at home in 1952, at age 68. There was no autopsy.

Case 7 (from the office records of Dr. Charles R. L. Halley, Clinical Professor of Medicine, The George Washington University). A white male veterinarian had had an intermittent febrile illness at age 36 which was diagnosed as brucellosis. Subsequently he had frequent rashes on the arms following placental extractions in cattle. At age 66 he had an intermittent febrile illness lasting five months. The serum agglutination test for Brucella was positive 1:10 on one occasion. Slight dyspnea developed during this illness, and a systolic murmur was heard over the whole precordium. Digitalis was begun and continued in small doses throughout life. At age 70 the patient had a sudden episode of hematemesis and was admitted to another hospital, where he died. Autopsy revealed a duodenal ulcer, and the entire gastrointestinal tract was filled with blood. The heart weighed 340 gm. The aortic valve showed calcification and rigidity of the right and posterior cusps at the commissure.

Case 8 (from the records of Dr. William D. Stroud of Philadelphia). A white female physician developed undulant fever in 1942 at the age of 44 years. The basis on which the diagnosis was made is not known, but she was sick intermittently for over a year. Apparently there was no suspicion of cardiac involvement during the course of this infection. In 1945, while driving her car, she was suddenly seized with an attack of suffocation, without pain, cough or sweating. She was hospitalized and oxygen therapy and other emergency measures were given, with good results. She was seen by Dr. Stroud some time later for evaluation of the cardiac status. The blood pressure was 170/60 mm. of Hg. The heart was enlarged and there was a systolic heave to the precordium. A systolic murmur was present at the apex, and systolic and diastolic murmurs were heard over the aortic area. Five weeks after this first visit sweats developed, and there was a suspicion that the brucellosis had recurred. The sweats subsided, however, and the patient refused to undergo the suggested studies. The physical evidence of aortic regurgitation persisted without change. Symptoms improved under therapy, and by September, 1945, the patient was able to return to work. She died a few months later. There was no autopsy.

Case 9. A white housewife had drunk raw milk all her life, and had worked with cattle on a farm during summer vacations. At age 60 to 61 there were recurrent periods of low grade fever. Serum agglutination for Brucella was negative, but a skin test with Brucellergen was strongly positive. The clinical diagnosis was brucellosis. A loud, harsh systolic murmur was heard at the apex and transmitted

to the vessels of the neck. The blood pressure was 205/85 mm. of Hg. Gradually the fever disappeared but the murmur persisted. Some months later a urinary tract infection developed and the patient was admitted to The George Washington University Hospital. A blood culture was positive for *Streptococcus faecalis*. The terminal illness was febrile.

At necropsy the heart weighed 420 gm. There were vegetations on the aortic valve, and from these vegetations the Streptococcus was again cultured. One of the valve cusps had ruptured. In addition, there were older hyaline fibrotic changes in the aortic valve cusps. This case is believed to be one of subacute bacterial (Streptococcus) endocarditis, superimposed upon an older valvular lesion due to brucellosis.

(This patient's husband, who had had the same exposure to brucellosis but no known infection, died from heart failure due to calcific aortic stenosis.)

Case 10 (from the office records of Dr. R. Bretney Miller, Associate in Medicine, The George Washington University). A white male physician had drunk raw "certified" milk all his life. In November, 1946, at age 43, he visited a rural inn and drank raw milk from a herd later shown to have Bang's disease. Twelve days later he developed a mild upper respiratory infection, laryngitis and slight cough. Shortly thereafter he noted a sense of fullness in his neck and upper mediastinum, with aching in this area. After about one week there was slight fever (99 to 100° F.), malaise, aching in the chest, shoulders and left elbow, and fatigue. Physical examination was essentially negative.

This was the beginning of a vague, intermittent, febrile illness which lasted, with many remissions, for five years. Blood cultures were repeatedly negative. The Brucella agglutination test was positive 1:80 once during the first year but was negative on other occasions. A skin test with Brucellergen was strongly positive, and resulted in an exacerbation of symptoms and fever of 101° F.

During August, 1951, at age 48, there were brief intervals of dizziness and blurring of vision, followed later by "black-out" spells. During these episodes the pulse rate slowed to 42 to 48; with recovery the pulse rate was 80 to 86. An electrocardiogram taken during stimulation of the left carotid sinus showed transient complete heart block; the test was followed by syncope. In September, 1951, there was a period of unconsciousness lasting about 30 minutes.

Because of experience with other cases of brucellosis, the senior author suggested that the new aspects of this case might be due to aortic stenosis. This was confirmed by arterial pulse tracings, and by the detection of a blowing, slightly harsh systolic murmur in the aortic area. With the development of an idioventricular rhythm, the Adams-Stokes episodes ceased and the patient resumed near-normal activities. At present (April, 1958) he is nearly free of symptoms. There has been no evidence of heart failure at any time, nor is there evidence of enlargement of the heart on x-ray. The systolic murmur can be heard over the whole precordium; it is maximal at the aortic area and radiates into the vessels of the neck. The aortic valve cusps show no calcification by roentgenographic examination.

Discussion

There is thus ample evidence, both from the studies of others and from our own cases, that the heart may be affected during the course of nonfatal brucellosis. In most instances of mild infection the heart probably returns to normal once the acute episode subsides. We have investigated a number of cases where the infection came from contaminated dairy products or from brief laboratory exposure to Brucella and have found none with certain evidence of residual heart disease.

Significant brucellar heart disease occurs chiefly in those having heavy and prolonged occupational exposure to the infection. Such patients may have relatively few symptoms in spite of recurring bacteremia. Thus they may continue at work, renew their exposure, and be repeatedly reinfected throughout life. One can hardly imagine a set of circumstances more likely to produce recurrent bacterial endocarditis.

Often these patients, when first seen, give a history of prior "rheumatic fever," or state that they have "rheumatic" heart disease. Such statements reflect prevailing concepts of the etiology of valvular heart disease. Obviously it would be impossible to distinguish rheumatic fever from brucellosis on the basis of the history alone.[21]

Some may be unwilling to accept the diagnosis of brucellosis in all of the cases we have presented, in spite of the heavy exposure to infection and the characteristic course of the illness. We agree that in some of these patients the diagnosis is not established beyond a doubt. In several the illness diagnosed as brucellosis had occurred many years ago, before the standardization of Brucella antigen and before the development of effective methods for the culture of Brucella.

It is important to emphasize that even with modern methods of laboratory diagnosis, in the hands of experts, some patients with positive blood cultures for Brucella will fail to develop antibodies, while others showing a high antibody titer will have repeatedly negative blood cultures. How many patients ill with brucellosis give negative results by both tests no one can say, but the number is probably large.

Brucellosis is not the only disease in which the diagnostic tests are inadequate and fallacious. In rheumatic fever also the diagnosis usually rests upon empiric evidence: "the clinical syndrome" [22] or the "Jones criteria." [23] There is no specific diagnostic test for rheumatic fever.

Others will question that the heart disease which developed in these patients following brucellosis was actually caused by brucellosis. This is, of course, impossible to answer precisely in a study of human cases. We can only indicate that the heart disease in the majority of the cases cited is of a specific anatomic and pathologic type: calcific aortic stenosis. This corresponds to the autopsy findings in fatal brucellosis: the valve predominantly affected is the aortic valve; the lesions are chronic and give pathologic evidence of a tendency to heal and calcify.[1]

Summary

Having noted the frequency and chronic nature of the endocarditis of the aortic valve in fatal brucellosis, we have searched for evidence that similar lesions may occur in patients who survive their infection. In the literature much evidence has been found to indicate that the heart may be affected in nonfatal brucellosis. By investigating a number of patients

presenting with evidence of calcific aortic stenosis, we have found four cases where an infection diagnosed as brucellosis preceded the recognition of valvular heart disease. Conversely, by studying a number of patients in whom a diagnosis of brucellosis had been made previously, we have uncovered six cases of chronic valvular heart disease. These 10 cases, none of whom died of brucellar infection, serve as the basis for this report. In nine of them the aortic valve was affected.

In most of the cases reported here there was a history of long occupational exposure to brucellosis, and it was frequently impossible to date the infection accurately. The average age at onset of brucellosis in these cases is estimated as 40.7 years. The average age at the time of diagnosis of heart disease was 51.5 years. The average age at death (six cases) was 59.5 years. Four of the patients are believed to be alive at the time of this report.

These 10 cases show that endocarditis due to brucellosis is not necessarily fatal during the phase of active infection, but has a natural tendency to heal. These cases provide the missing link in the chain of evidence which connects brucellar endocarditis to calcific aortic stenosis.

Further evidence in support of this concept is presented in the fourth paper in this series.[18]

Summario in Interlingua

Brucellosis es rarmente letal, sed quando illo lo es, le morte resulta usualmente de endocarditis. Mortal endocarditis brucellari es characteristicamente chronic e affice principalmente le valvula aortic. Le lesiones valvular tende a calcificar se, mesmo quando le bacteremia persiste, e le morte resulta usualmente de disfallimento cardiac plus tosto que de embolismo o de sepsis.

Le natura chronic de mortal endocarditis brucellari induceva nos a cercar evidentia de un residue morbo cardiac valvular in patientes qui se habeva restablite ab brucellosis. Dece tal patientes esseva trovate. Le detalios de lor curso clinic es le substantia del presente reporto. In omne iste casos le diagnose de brucellosis esseva facite alterubi. In plure casos le confirmation laboratorial esseva adequate, sed in alteres nulle tal confirmation existeva. Nulle demonstration de brucellas per methodos de culturation habeva essite effectuate in ulle del casos. Tamen, le constatationes in le 10 casos esseva simile a illos in culturalmente demonstrate casos de brucellosis mortal. Le affection predominante interessava le valvula aortic, e le processo pathologic pareva esser essentialmente le mesme.

Le problema del diagnose de morbo cardiac brucellari es principalmente concernite con le differentiation inter brucellosis e febre rheumatic. Le tests laboratorial pro brucellosis non es necessarimente positive in omne le patientes in qui iste morbo es demonstrate subsequentemente. Quando morbo cardiac valvular occurre in un patiente de etate adulte e quando le valvula interessate es primarimente le valvula aortic, le suspicion de morbo cardiac brucellari es indicate.

Le 10 casos hic reportate demonstra que endocarditis causate per brucellas non es necessarimente mortal. Assi illos claude un lacuna que existeva usque nunc in le continuitate del documentation. Datos additional in supporto de iste conception es presentate in le quarte articulo de iste serie.

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REGIONAL ENTERITIS. I. CLINICAL ASPECTS AND DIAGNOSIS IN 100 PATIENTS *†

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ALTHOUGH regional ileitis was recognized as a clinical entity by Crohn, Ginsburg and Oppenheimer [1] 26 years ago, much remains unknown concerning the etiology, pathogenesis and treatment of the disease.

Regional ileitis was defined by Crohn, Ginsburg and Oppenheimer [1] as a recurrent granulomatous disease mainly affecting young adults. In the acute inflammatory phase, ulcerative lesions are prominent; later, thickening of the mucosa, scarring, intestinal obstruction and fistulas may be present. The terminal ileum chiefly is involved, although lesions may be present elsewhere in the small intestine. Regional enteritis may cross the ileocecal valve and involve the colon (ileocolitis). The disease is characterized clinically by abdominal cramps, signs of obstruction, diarrhea, fever, loss of weight and anemia, and by the presence of an abdominal mass, perianal abscesses, and fistulas.

The etiology of regional enteritis remains obscure. Multiple factors have been implicated, including bacteria (especially the tubercle bacillus), heredity, psychosomatic disorder, metabolic dysfunction and allergy. The evaluation of the etiology is difficult because some of these factors may have a synergistic effect in the production of the lesion. The frequent finding of a block of the intestinal lymphatics and lymphadenopathy suggests a relationship to connective tissue or collagen disease. Crohn [2] points out that the histopathologic characteristics of Boeck's sarcoid and of ileitis are almost identical. The results of Kveim tests in four of our patients with regional enteritis, however, were negative.[3] Psychosomatic factors are less important in regional enteritis than they are in chronic ulcerative colitis. Patients with regional enteritis do not present the same type of personality or of personality problems as do those with ulcerative colitis; in addition, acute flare-ups of the disease do not seem to be precipitated by acute emotional crises, as they are in acute ulcerative colitis.

Large series of cases have been reported by Van Patter and associates [4] and by Crohn.[2] Rossmiller and Messenger [5] reviewed the findings in 55 patients with regional enteritis who were seen at the Cleveland Clinic from

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1937 to 1946. It is the purpose of the present report to review findings in 100 patients with the disease who were seen here during the 11-year period from 1946 through 1956.

Clinical Aspects

Incidence: Males are slightly more susceptible to regional enteritis than are females. In the present series there were 53 males and 47 females. This distribution agrees with those of most other reports, where males constitute approximately 55% of the patients.

Meyers, Ruble and Ashley [6] and others have noted that the disease is infrequent in Negroes, in persons of low-income groups, and in charity hospitals, and is more frequent in persons of middle- and high-income groups, in private hospitals, and in Hebrews.

The disease is predominantly one of young adults: 55% of our patients were less than 31 years of age (table 1). However, 15% of our patients

Table 1

Age of 100 Patients at the Onset of Symptoms of Regional Enteritis

Age at Onset, years	Number of Patients
16–20	13
21–25	27
26–30	15
31–35	12
36–40	8
41–45	9
46–50	1
51–55	6
56–60	2
61–65	5
66–70	2

were more than 50, and 11% of the 100 patients reported by Meyers and associates [6] were more than 50 years of age when symptoms were first noted.

Symptoms: Symptoms of the disease may be present for a long time before diagnosis. Many of the symptoms are nonspecific, such as mild fever, anemia or mild diarrhea, and may not suggest the possibility of this condition until some complication, such as fistulas, obstruction or gastrointestinal bleeding, occurs. Forty-three of our patients had had symptoms for less than 12 months, and 26 had had symptoms for more than four years before diagnosis (table 2). The average duration of symptoms before diagnosis was 2.9 years. The long duration of symptoms before diagnosis demonstrates the insidious character of this disease; frequently, the correct diagnosis was made only after complications had developed.

Frequently, the onset of regional enteritis consisted of occasional attacks of diarrhea, fever, or formation of fistulas in the abdominal wall or around the rectum. Occasionally, the symptoms started after gastrointestinal "flu" or dietary indiscretion. In two patients symptoms began after an auto-

TABLE 2

Duration of Symptoms Before Diagnosis of Regional Enteritis in 100 Patients

Duration of Symptoms	Number of Patients
0 to 6 months	24
6 to 12 months	19
1 to 2 years	13
2 to 4 years	18
4 to 6 years	14
6 to 8 years	3
8 to 10 years	5
10 to 20 years	4
Average: 2.9 years	100

mobile accident, in two after recovery from amebiasis, in one during pregnancy, in one post partum, in one after recovery from paratyphoid fever, and in one after an emotional crisis in the family. In contrast, the acute toxic attack of ulcerative colitis frequently is precipitated by emotional factors. Recurrences of regional enteritis frequently have followed acute upper respiratory infection.

The incidence of the various symptoms in our patients is shown in table 3. It should be stressed that many patients initially had only one symptom, and that few had all the symptoms listed. However, the presence of any one of these symptoms should indicate the possibility of regional enteritis.

Colic or abdominal pain was present in 88 of our patients. This pain usually was cramplike and colicky, but in a few patients it was continuous. The pain was located either in the right lower quadrant or periumbilically. Few conditions other than small-intestinal lesions cause periumbilical pain. The pain frequently was relieved by passing flatus or by defecation; this relief was so marked in two patients that they kept themselves in a chronic state of diarrhea by the use of strong laxatives. The colicky type of pain frequently was aggravated by eating, which is one reason for the loss of weight in these patients. The cramping pain usually was associated with partial obstruction, caused either by inflammatory swelling in the acute stage, or by scarring in the later stages of the disease. Frequently patients complained of attacks of the cramping pain lasting for from one to several days, with freedom from distress between the attacks. Such attacks have been precipitated by high-residue foods such as corn and nuts.

TABLE 3

Symptoms in 100 Patients with Regional Enteritis

Symptom		Number of Patients
Colic or abdominal pain		88
Diarrhea		81
Loss of weight		70
Gastrointestinal bleeding		34
Streaking in stool	24	
Profuse red blood in stool	6	
Tarry stools	4	
Draining sinus		33
Fever		32
Fistula-in-ano		14

The continuous pain usually occurred in the right lower quadrant and was associated with tenderness to palpation, inflammation of the bowel or intestinal peritoneum, and abscess or fistula formation.

Diarrhea was present in 81 of our patients. The number of movements and intensity of the diarrhea rarely approached that of ulcerative colitis. These patients usually had daily two to five mushy, poorly formed or liquid stools that contained some mucus and sometimes blood. Bowel movements were frequently preceded by abdominal pain and rumbling, the so-called *predefecation pain,* which was relieved by defecation. While 81 of our patients had diarrhea, 14 had no change in bowel habits. Three patients had constipation which was not associated with obstruction but had been present before the onset of other symptoms ascribed to regional enteritis. Two patients had diarrhea alternating with constipation.

Loss of weight occurred in 70 of our patients. Weakness and loss of strength and energy sometimes were associated with the weight loss. The average loss of weight was 15 pounds, but five patients had lost more than 30 pounds and were severely malnourished. Of these five patients, two had chronic intestinal obstruction, two had fecal fistulas after operation elsewhere, and one had a subacute perforation of the intestine.

Gastrointestinal bleeding was reported by 34 patients. Twenty-four had red streaking of the stools resulting from the hyperemic, eroded mucosa. Profuse red blood in the stool was reported by six patients with ileocolitis. Tarry stools were noted by four patients, two of whom had extensive ileitis, one ileojejunitis, and one ileocolitis with a duodenal ulcer. Meyers, Ruble and Ashley [6] reported that 4% of their patients had gross hemorrhage from the bowel.

Fever was present on initial examination in 20 patients, and 12 other patients had had febrile episodes. In several patients fever was the only symptom, and it had been classified as "fever of unknown etiology" for some time before the correct diagnosis was made. Temperature was 99.6 to 100.5° F. in nine patients, 100.6 to 102.6° F. in seven patients, and 102.7 to 104° F. in four patients. Extreme elevation of temperature was associated with severe or extensive inflammation and complications such as fistulas and abscesses.

Physical Examination: The findings on physical examination of the 100 patients are presented in table 4.

The most frequent finding was the presence of fistulas (48 patients). The perianal type of fistula is the most common and was present in 21 of our patients. These fistulas may develop subsequent to infection of an anorectal crypt, or by direct extension from the inflamed ileum which descends into the cul-de-sac. A perianal fistula may be the patient's only complaint. Crohn [2] pointed out that suppurative perianal fistulas in the presence of diarrhea indicate an inflammatory process somewhere in the intestinal tract, most frequently ileitis, ulcerative colitis and intestinal tuber-

TABLE 4

Findings on Physical Examination of 100 Patients with Regional Enteritis

Finding		Number of Patients
Fistulas		48
Perianal	21	
External	12	
Internal	11	
External, internal	4	
Mass		35
Abdominal	32	
Rectal	2	
Pelvic	1	
Signs and symptoms of obstruction		30
Abscess		15
Intra-abdominal	10	
Perianal	5	

culosis. External fistulas to the anterior abdominal wall were present in 12 of our patients, and occurred at the site of a scar of a previous laparotomy, usually an appendectomy. They usually developed within a few weeks after the operation. Internal fistulas between loops of bowel or other hollow viscera were present in 11 of our patients. These fistulas involved the ileum and sigmoid in three patients, the ileum and colon and the ileum and rectum and vagina in two patients, the ileum and cecum in one patient, the ileum and bladder in one patient, and loops of ileum in one patient.

An abdominal mass was present in 35 of the 100 patients. The mass occurred most frequently in the right lower quadrant (29 patients), but occurred in the epigastrium, in the midabdomen, in the left lower quadrant, and in the pelvis in one patient each. A mass was found by rectal examination in two patients. The mass frequently represented the inflamed terminal ileum, which might become adherent to other loops of small intestine, to the colon, or to the bladder. In some cases the mass was an abscess associated with formation of fistulas.

Partial obstruction of the small intestine was present in 30 patients. In some this obstruction caused vomiting, abdominal cramps or frequent gurgling in the abdomen. Physical examination in these patients showed a distended abdomen, frequently visible peristaltic waves, and increased peristaltic activity on auscultation of the abdomen.

Perianal abscesses were present in five patients, while intra-abdominal abscesses, usually associated with fistulas, were present in 10 patients. Five of the intra-abdominal abscesses were located in the right lower quadrant, two in the periappendix, one in the right psoas muscle, and two in the pelvis.

Anatomic Distribution in Regional Enteritis: In our series of 100 cases the extent of intestinal involvement was noted in all patients (table 5). It was impossible to state the exact original anatomic involvement in patients who were operated upon elsewhere. In patients who were not operated

upon, we relied on the roentgen findings to determine the extent and location of the disease.

Patients who primarily had ulcerative colitis with a "backwash" ileitis were excluded from this study. Thirty-seven of our patients had ileocolitis,[7] but the primary pathologic condition in these patients was ileitis rather than colitis. The extent of the involvement of the colon was limited to the ascending colon in 11 and to the cecum in four of the patients with ileocolitis. The sigmoid colon only was involved in three patients with ileocolitis, probably by contiguous spread from the diseased ileum.

In this series of 100 patients, only two had no involvement of the ileum. A 16 year old girl who complained of intermittent attacks of periumbilical pain was found to have regional enteritis limited to the midjejunum, with no disease in the ileum. In another patient, reported previously,[8] the disease was limited to the second portion of the duodenum, causing duodenal and gastric obstruction and vomiting. Duodenojejunostomy relieved the latter patient's symptoms, and she has remained asymptomatic for six years after operation.

In two other patients the disease involved the duodenum in addition to the terminal ileum. In one of these patients the stomach may have been involved as well, since the gastric mucosa was thickened. Gastrojejunostomy and vagotomy were performed in both of these patients to relieve the duodenal obstruction, and resection of the terminal ileum and right colon was performed in one.

The frequent involvement of the ileum in regional enteritis (in 98 of our cases) is of considerable help clinically and diagnostically. Because of this predominant location of the disease, symptoms are usually referred to the right lower quadrant. Thirty-two of our patients had had an appendectomy, while 187 of the 600 patients reported by Van Patter and associates [4] had had an appendectomy. A mass was present in the right lower quadrant in 29 of our patients.

Because of the high incidence of the disease in this location, a barium enema study of the colon which showed a normal-appearing ileum would indicate that regional enteritis probably is not present. The disease may involve any location in the small intestine, but the chances of a patient's

TABLE 5

Location of Disease in 100 Patients with Regional Enteritis

Location of Disease	Number of Patients
Terminal ileum	39
Ileum and jejunum, extensive in ileum	20
Ileum and colon	19
Ileum, cecum and ascending colon	11
Ileum and cecum	4
Ileum and sigmoid colon	3
Ileum and duodenum	2
Duodenum only	1
Jejunum only	1

having regional enteritis are remote if the terminal ileum is normal. When the terminal ileum is not filled on barium enema examination, this study is of no help in ruling regional enteritis either in or out.

Systemic Complications: Systemic complications in regional enteritis are in general less frequent and less severe than those in ulcerative colitis. The systemic complications in our patients are presented in table 6.

Eight patients in our series had signs of acute or subacute arthritis. In six of these patients, swelling and pain involved mostly the small, especially the phalangeal, joints or the joints of ankles and wrists. Two patients had severe rheumatoid spondylitis. It is of interest that, of the eight patients, six had ileocolitis, while the disease was limited to the small intestine in two.

Arthritis is less frequent in regional enteritis than it is in ulcerative colitis. Crohn [2] reported joint pains in four of 222 patients with regional enteritis, while Van Patter and associates [4] found rheumatoid arthritis in about 4% of their 600 patients. The smaller joints of the extremities and occasionally the vertebral column were involved. The severity of the arthritis seems to parallel the activity of the intestinal disease. When arthritis recurs after resection of the terminal ileum, it may indicate recurrence of the regional enteritis.

TABLE 6

Systemic Complications in 100 Patients with Regional Enteritis

Complication		Number of Patients
Rheumatoid arthritis		8
Small joints, extremities	6	
Spondylitis	2	
Vitamin deficiency		5
Clubbing of fingers		3
Erythema nodosum		2
Iritis and iridocyclitis		2
Periarteritis nodosum		1
Episcleritis		1
Choroiditis		1

In five cases in our series there were signs of vitamin deficiency. One patient complained of a painful tongue, which was red and atrophic. She responded well to treatment with vitamin B_{12}. Another patient had rhagades around the mouth. A third patient had skin changes associated with emaciation and hypoproteinemia. The fourth patient had absent tendon reflexes in the legs, possibly associated with regional enteritis, while the fifth patient had subacute sclerosis with extensive regional enteritis and partial obstruction of the small bowel. The patients with vitamin deficiencies also showed evidence of malnutrition.

Three patients had clubbing of the fingers or pulmonary osteoarthropathy. One of these patients had recurrent intestinal obstruction and had lost 35 pounds in weight during the previous six months.

Erythema nodosum may occur in patients with regional enteritis. Van Patter and associates [4] reported this complication in five of 600 patients, and

Crohn [2] in three of 222 patients with regional enteritis. Each of our two patients who had had this complication underwent resection of the terminal ileum and has been free from symptoms of either the erythema nodosum or the regional enteritis for three and five years after operation, respectively.

Recurring attacks of iritis and iridocyclitis were the chief complaints in two patients with regional enteritis limited to the terminal ileum. With medical treatment (including steroids, sulfa preparations and antibiotics), both have improved.

Periarteritis nodosa was reported on biopsy of an erythema nodosum-like lesion in another patient who also had episcleritis. Resection of the terminal ileum in this patient was followed by healing of the eruption and of the episcleritis.

One patient developed choroiditis coincident with the onset of the diarrhea associated with the regional enteritis.

Pathologic Findings

Of the 100 patients in this series, 65 were operated upon, 48 having resection of the small intestine at the Cleveland Clinic. The following pathologic description is based on the findings in these 48 patients.

Grossly in the acute stage, the involved part of the intestine appeared to be bright red to dusky blue, with a fibrinous exudate over the lesion. Chronic lesions were a more normal color but with many adhesions, sometimes so thickened with fibrous tissue that they felt like a scirrhous carcinoma. The thick adhesions sometimes resulted in a matting together of several intestinal loops. The mesentery also was thickened, and the surrounding lymph nodes were enlarged. The wall of the intestines was thickened, sometimes resulting in a narrow intestinal channel and partial obstruction (30 cases). Internal fistulas were present in 11 patients, external fistulas to the right lower quadrant in 12 patients, and both internal and external fistulas in four patients. Abscesses were present in 13 patients.

When the intestine was opened, the edema of the mucous membranes in the acute stage was particularly prominent. Ulcers frequently were present along the mesenteric attachments; nonulcerated mucosal islands produced a cobblestone appearance. The gross lesion in the intestinal wall terminated rather abruptly. "Skip" lesions, with normal intestine between areas of diseased bowel, were present in 16 patients.

The most characteristic microscopic findings in regional enteritis were those in the submucosa. Interstitial edema, lymphoid hyperplasia, and distention and thickening of the submucosa were most marked. Another prominent feature was the presence of granulomatous lesions, i.e., small epithelioid, tubercle-like nodules with occasional giant cells. Similar but less pronounced changes occurred in the serosa, mesentery, and in the lymph nodes.

Roentgen Findings

If the terminal ileum is visualized on barium enema study, the findings on this examination frequently can be the basis for the diagnosis. The loss of the normal mucosal pattern in the terminal ileum is suggestive, and the narrowed "string" sign in more chronic cases is diagnostic. We believe that barium enema study should be done prior to small-intestinal motility studies; the diagnosis can frequently be made by this simpler study, and the possibility of obstruction can be excluded.

A comparison between the findings on barium enema and on small-bowel motility studies is of interest. The findings on both studies were diagnostic or suggestive in 55% of the patients. Findings on barium enema examination alone were diagnostic in 28%. Results of motility studies were positive (no barium enema examination) in 11%. Results of motility studies were diagnostic and findings on barium enema examination were negative in 4%, while results of motility studies were negative and findings on barium enema examination were positive in 2%. Consequently, findings on barium enema examination were diagnostic in 85% and falsely normal in 4% of the 100 patients; 11% of the patients did not undergo the examination.

The predominant roentgen findings were: narrowing and mucosal changes (31 patients); mucosal changes alone (23); narrowing with some dilatation proximally (20); and definite obstruction (10). Fistulous tracts were demonstrated in only 10 patients, although a total of 27 had internal or external fistulas, or both. Filling defects were noted in six patients. Fistulas were demonstrated by roentgen study in only slightly more than one third of the patients (10 of 27) who had fistulas.

Small-intestinal motility studies [9] are indicated in those patients in whom there are suspicious clinical findings and in those in whom the terminal ileum appears to be abnormal on barium enema study (figures 1, 2, 3, and 4). The small intestine is the most difficult portion of the gastrointestinal tract to examine roentgenographically, and frequently severe disease and partial obstruction must be present before the roentgen findings are diagnostic. A small amount of barium followed by frequent films for the next six to eight hours and another film in 24 hours may demonstrate a loop of dilated small intestine, multiple areas of narrowing as in "skip" areas, or a "string" sign—all suggestive of regional enteritis. A prolonged delay of barium (two to four hours) in one segment of small intestine should make one suspicious of partial obstruction, even though the area of obstruction is not visualized. We have seen several patients with histories suggestive of attacks of intermittent obstruction in whom motility studies were normal until they were obtained during such an attack.

Diagnosis

Any one of the following symptoms or findings should at least indicate the possible presence of regional enteritis: right lower quadrant or perium-

bilical pain, either constant or cramplike and colicky; diarrhea; loss of weight; unexplained fever; gastrointestinal bleeding or unexplained anemia; an abdominal mass, and fistulas. A patient may initially present only one of these symptoms. It should not be necessary to await the typical picture of emaciation, an abdominal mass, a fistula and evidence of obstruction be-

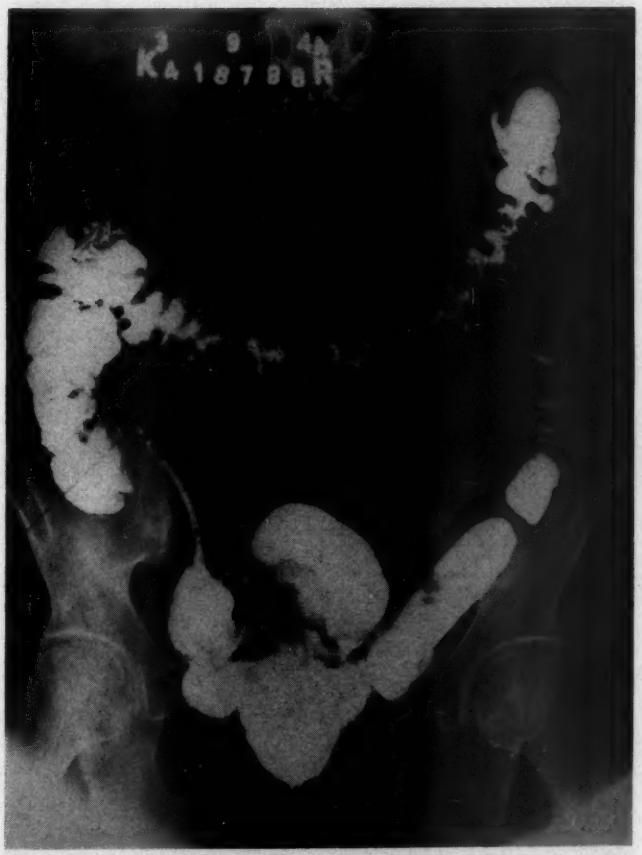

FIG. 1. Typical "string sign" or narrowing of the terminal ileum seen by barium enema examination in a patient with regional enteritis.

fore the diagnosis is made. The greater the number of the abovementioned symptoms and findings in a patient, the greater should be the suspicion that regional enteritis is present.

In the differential diagnosis, other causes of periumbilical and right lower quadrant pain, diarrhea, gastrointestinal bleeding and anemia, fever, an abdominal mass, fistula and partial obstruction of the small intestine must

be considered. To make an accurate diagnosis, the following studies should be made: complete history and physical examination; proctosigmoidoscopic examination; laboratory studies, including urinalysis, complete blood count, agglutinations for dysentery organisms, warm-stage stool examination, culture of the stool and any draining abscess or fistula, and sometimes an L.E.

FIG. 2. Long segment of narrowing of the distal ileum visualized on motility studies. There is no evidence of obstruction. Resection was performed, but did not relieve the symptoms of cramplike abdominal pain and mild diarrhea that had been present for 25 years and were considered to be functional.

(lupus erythematosus) test, Kveim test, undulant fever agglutinations and skin test, and other special studies; roentgen examinations of the chest, flat plates of the abdomen (to detect intestinal obstruction), barium enema examination of the colon and, finally, motility studies of the small intestine.

However, even after the abovementioned examinations have been made

there will remain a small group of patients in whom only a provisional diagnosis can be made clinically, and operation is necessary for the final diagnosis. This is particularly true of those patients in whom the only finding is that of small-bowel obstruction due to chronic stenosing regional enteritis. Nonetheless, a high degree of awareness of the clinical picture of regional enteritis should result in earlier diagnosis of the disease.

FIG. 3. Film taken three hours after ingestion of barium, showing multiple skip areas of regional enteritis. No obstruction was present. The skip areas involved only the ileum; the remainder of the small intestine was normal.

SUMMARY

The findings in 100 patients with regional enteritis who were seen at the Cleveland Clinic from 1946 through 1956 are the basis of this report. The specific etiology of the disease is not yet known.

The disease predominantly affects young adults (55% of our patients were less than 31 years of age), although it also occurs in older patients (15% of our patients were more than 50 years of age).

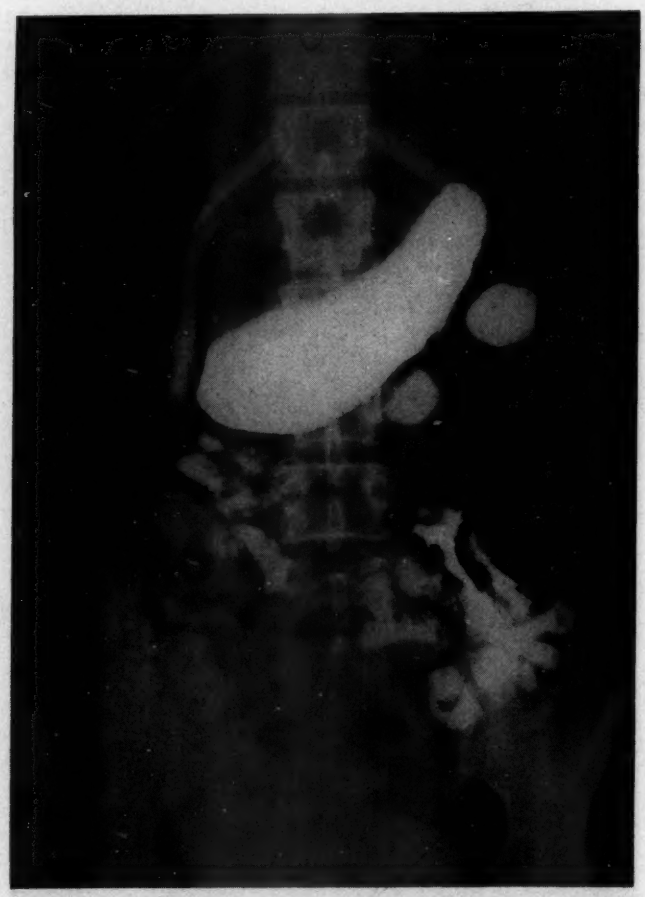

FIG. 4. Motility study showing obstruction and dilatation of the small intestine due to regional enteritis. One year previously this patient had been told elsewhere that she had a "nervous bowel." She had lost 40 pounds in weight, which she regained after small-intestinal resection.

The symptoms initially may be mild and may be present for a long time before diagnosis; the average duration of symptoms in our patients was 2.9 years. The chief symptoms in our patients were: colic or abdominal pain (88 patients); diarrhea (81); loss of weight (70); gastrointestinal bleeding (34); draining sinus (33); fever (32), and fistula-in-ano (14). A patient

may present only one of the symptoms, especially early in the course of the disease.

Physical examination showed fistulas in 48 patients, an abdominal mass in 35, signs and symptoms of partial obstruction of the small intestines in 30, and abscesses in 15. The ileum was involved in 98 patients.

Systemic complications were not so frequent as they are in ulcerative colitis, and usually subsided with adequate treatment of the underlying disease.

Roentgen examination of these patients initially should include a flat plate of the abdomen (to detect possible obstruction), followed by barium enema study. Since the ileum is so frequently involved (98 of our cases), findings on barium enema study may be diagnostic. Motility studies of the small intestine should then be done to determine the degree and extent of the disease.

The diagnosis of regional enteritis could be made earlier in the course of the disease if there were a greater awareness of the signs and symptoms of the disease. A patient may have only one of the typical symptoms or findings, but that alone should indicate the possible presence of regional enteritis. The greater the number of those typical symptoms or findings in a patient, the more likely is the diagnosis to be regional enteritis. If the clinical findings strongly suggest regional enteritis, the diagnosis should be made even when the roentgen findings are normal.

Summario in Interlingua

Le base del presente reporto es le constatationes facite in le casos de 100 patientes con enteritis regional vidite al Clinica Cleveland ab 1946 usque al fin de 1956. Le etiologia specific del morbo non es cognoscite.

Le morbo affice predominantemente adultos de juvene etate (55% de nostre patientes habeva minus que 31 annos de etate, sed illo etiam occurre a etates plus avantiate (15% de nostre patientes habeva plus que 50 annos de etate).

Le symptomas initial es frequentemente leve. Illos pote durar longemente ante que le diagnose es establite. Le duration medie del symptomas in nostre patientes esseva 2,9 annos. Le symptomas principal in nostre patientes esseva: Colica o dolores abdominal (88 casos); diarrhea (81); perdita de peso (70); sanguination gastrointestinal (34); sinus a drainage (33); febre (32); e fistula in ano (14). Il occurre que un patiente exhibi solmente un de ille symptomas, specialmente durante le prime phases del morbo.

Le examine physic revelava fistulas in 48 patientes, un massa abdominal in 35, signos e symptomas de obstruction partial del intestino tenue in 30, e abscessos in 15. Le ileum esseva afficite in 98 patientes.

Le complicationes systemic esseva minus frequente que in colitis ulcerative. Usualmente illos subsideva con le tractamento adequate del morbo subjacente.

Le examine roentgenologic de iste patientes debe includer initialmente un platta plan del abdomine (pro deteger le presentia possibile de un obstruction), sequite per un studio a clyster de barium. Viste que le ileum es afficite si frequentemente (98 de nostre casos), le constatationes del studio a clyster de barium pote esser diagnostic. Studios del motilitate in le intestino tenue debe esser effectuate pro determinar le grado e le extension del morbo.

Il esserea possibile establir le diagnose de enteritis regional plus precocemente in le curso del morbo si le alertia pro le signos e symptomas del morbo esseva plus general. Un patiente pote haber non plus que un sol del typic symptomas o constatationes, como per exemplo febre o anemia, sed isto suffice per se a indicar le presentia possibile de enteritis regional. Quanto plus grande le numero de tal typic symptomas o constatationes in un patiente, tanto plus probabile le diagnose de enteritis regional. Quando le constatationes clinic suggere fortemente le presentia de enteritis regional, ille diagnose debe esser facite mesmo si le constatationes roentgenologic es normal.

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REGIONAL ENTERITIS. II. RESULTS OF MEDICAL AND SURGICAL TREATMENT IN 100 PATIENTS*

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THE nature and etiology of regional enteritis are obscure. Because some patients have repeated recurrences, with multiple "skip" lesions and extensive involvement of the small intestine, physicians generally are pessimistic concerning long-term results of treatment of the disease.

There are uncertainties about the effectiveness of medical treatment, little having been published on this form of treatment, and there is disagreement about the preferred surgical treatment of the disease. Some surgeons recommend a side-tracking operation with exclusion (ileotransverse colostomy with transection of the ileum), and others recommend resection of the diseased intestine; however, over-all results of the two procedures have been similar.

On the basis of the results of treatment in 100 patients having moderately severe regional enteritis who were seen at the Cleveland Clinic from 1946 through 1956, we believe that pessimism concerning treatment of this disease is unwarranted. It is the purpose of this paper to report the results of treatment in these 100 patients, 35 of whom received only medical treatment and 65 of whom underwent operation.

To facilitate the discussion, the various grades of response to treatment among our patients have been categorized as follows: "good response"—patient is able to return to normal activity with no diarrhea or other symptoms; "fair response"—patient is able to continue in his regular occupation with a moderate limitation of activity and infrequent recurrence of symptoms; "poor response"—patient has frequent and disabling recurrences of symptoms. Results of treatment were considered "satisfactory" in patients in whom the response was "good" or "fair."

The clinical findings and diagnosis in these patients were summarized in Part I of this paper. The duration of follow-up is indicated in table 1.

MEDICAL TREATMENT

During the period of study, and now, it has been the policy at the Cleveland Clinic to treat patients with regional enteritis conservatively or medically unless there are urgent surgical indications or complications such as obstruction, fistula, abscess or severe gastrointestinal hemorrhage. If the

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TABLE 1

Duration of Follow-Up of 100 Patients with Regional Enteritis

Duration of Follow-Up	Number of Patients
Less than 1 year	14*
1 to 2 years	19
2 to 3 years	7
3 to 4 years	11
4 to 5 years	8
5 to 6 years	10
6 to 8 years	10
8 to 10 years	11
10 to 12 years	10

* Findings in these 14 patients are not included in this report; the duration of follow-up in the remaining 86 patients averaged 5.2 years.

patient does not respond to medical treatment, operation is advised. The fact that medical treatment may be beneficial and may obviate operation is indicated by Meyers, Ruble and Ashley's [1] report of 28 patients treated medically, 11 of whom were asymptomatic four to nine years and seven of whom were asymptomatic 10 to 18 years after diagnosis.

Medical treatment of regional enteritis in general is similar to that of ulcerative colitis.[2, 3] Multiple measures are used. The tendency is to try everything that could possibly help these patients, but as a consequence the results of a specific type of treatment are most difficult to establish. To evaluate the results of steroid, of roentgen, or of antituberculous treatment, controlled studies and prolonged follow-up would be essential.

All patients were given a low-residue, low-fat diet that was high in proteins, carbohydrates and vitamins. High-residue foods can cause obstruction in a narrowed ileum and must be avoided; one of our patients had four episodes of obstruction, all precipitated by corn and all relieved by medical treatment. Because nutrition is poor in patients with enteric disease, a high-caloric diet with supplementary protein feedings frequently was given. Large doses of vitamins, particularly vitamin B complex, were given orally, and occasionally liver extract, vitamin B complex, and B_{12} were given parenterally.

Mild sedation was used to help the patient get additional needed rest, and one of the antispasmodic or the anticholinergic drugs was given to decrease intestinal motility and spasm. Each patient received superficial psychotherapy from the gastroenterologist, but intensive psychiatric treatment was not given. One of the nonabsorbable sulfa preparations, such as Sulfasuxidine, Sulfathalidine or Azulfidine, was prescribed for most patients. Those drugs were given in doses of 1 gm. four times daily, either continuously or intermittently (administered for two weeks, not administered for one week, etc.). Although these preparations seemed to have a somewhat beneficial effect, they were not so helpful as in patients with ulcerative colitis. The beneficial effect of these drugs may result from their action on secondary bacterial invasion of the small bowel or on bacterial contamination of the ulcers.

Antibiotics: Crohn [4] in 1955 reported that the administration of Chloromycetin produced good results, and that streptomycin was helpful in the treatment of acute regional enteritis. Kirsner [5] also believed that streptomycin was helpful. Both authors warned that Aureomycin hydrochloride and Terramycin in themselves are capable of producing diarrhea, changes in the intestinal flora, and an overgrowth of monilia or staphylococci. In four of our patients the administration of Terramycin produced none of those untoward effects and was of definite benefit.

The tubercle bacillus or a similar organism had been considered as a possible etiologic agent in regional enteritis, but Meyers, Ruble and Ashley [1] reported that the administration of large doses of streptomycin and of isoniazid, which is effective in the treatment of tuberculosis, was of no benefit in regional enteritis. We have not used isoniazid in the treatment of regional enteritis because that drug is irritating to the gastrointestinal tract, but we have administered streptomycin, 1 gm. once weekly, over prolonged periods (one to three years) to five patients, all of whom remained relatively asymptomatic during that time. Administration of this drug had to be stopped in two other patients because of reactions to the medication.

Steroids: Varying results of steroidal therapy for regional enteritis have been reported.[5-14] Willard [15] recommended that antibiotics be administered simultaneously with the steroids. We concur with this recommendation, since the pathologic features of regional enteritis (the granulomas, lymphadenopathy, fistulas, abscesses) suggest that the condition may be an infection.

Twelve of our patients received steroidal therapy and, as Willard recommended, that therapy usually was supplemented by administration of one of the nonabsorbable sulfa preparations and one of the antibiotics, most often streptomycin. Two of the patients were lost to follow-up, and the administration of the drug was stopped as a precautionary measure in two others because of gastrointestinal bleeding, although in neither was the bleeding severe nor was an ulcer crater demonstrated. Since five of the remaining eight patients responded satisfactorily to steroidal therapy and there were no serious side-effects in any of the patients (table 2), we believe

TABLE 2

Steroidal Therapy in Regional Enteritis

Response*	Number of Patients	Recurrences	Complications of Therapy
Good	2	None—3 and 4 years	None
Fair	3	1—recurrence in 3 years 2—recurrence in 1 year	None
Poor	2	1—recurrence in 2 months 1—recurrence in 4 weeks	1—gastrointestinal bleeding—drug stopped
None	3		1—gastrointestinal bleeding—drug stopped

* Please see text for definition of grades of response.

that this therapy is definitely indicated in selected cases of regional enteritis. It may be of the most value in those patients with a spruelike or malabsorption syndrome.

Roentgen Therapy: Crohn [16] reported that roentgen therapy produced poor results in patients with regional enteritis. Popp, Bargen and Dixon [17] described the use of roentgen treatment at the Mayo Clinic in 1950. In the 55 patients reported by Van Patter and associates,[18] the results of roentgen therapy were good in 15 and fair in eight; the remaining 32 patients required operation, or died from their disease, or were lost to follow-up. Sauer and Ensrud [19] reported good response to roentgen therapy in six of eight patients; the two other patients died of the disease.

Six of our patients received roentgen therapy, one patient being given two courses (table 3). Two of the three patients who obtained a good result from the therapy had had two operations each for regional enteritis prior to the roentgen therapy. Since all three of these patients also received the other forms of medical treatment, including long-term use of streptomycin, it is difficult to evaluate the effect of any one facet of the program.

TABLE 3

Roentgen Therapy in Regional Enteritis

Response*	Number of Patients	Recurrence
Good	3	None in 1, 3 and 4 years, respectively
Poor	2	1—intestinal obstruction after therapy 1—rectal bleeding after therapy
None	1	

* Please see text for definition of grades of response.

Although roentgen treatment seemed most effective in the acute ulcerative phase of the disease resulting from lymphoid hyperplasia and lymphocytic infiltration, definite improvement has been reported in only a few patients. As Willard [15] noted, the post-treatment incidence of intestinal obstruction or increased diarrhea is high.

Over-All Results of Medical Treatment: As mentioned previously, there have been few reports on the effect of medical treatment in regional enteritis. Meyers, Ruble and Ashley [1] obtained good results with conservative therapy in 20 of 28 patients. Sauer and Ensrud [19] reported the results of medical treatment in 38 patients, 19 of whom had extensive disease (involving more than three feet of small intestine, skip areas, or internal fistulas). The duration of follow-up ranged from four to 15 years. In 19 of the 38 patients the response was good, and in 10 it was fair; thus in 29 (76%) of the patients the results were satisfactory. One patient was a chronic invalid, and eight patients died of the disease from 3.5 to 11.5 years after onset. Sauer and Ensrud stated that nonspecific conservative management was of definite benefit and deserved a trial unless there were complications of obstruction or fistulas.

TABLE 4

Results of Medical Therapy

Response*	Number of Patients
Good	14
Fair	9
Poor	3†
Insufficient follow-up (less than 1 year)	9

* Please see text for definition of grades of response.
† Operation proved necessary in two of these patients.

The results of medical treatment in the 35 patients in our series who received that treatment alone are summarized in table 4. The group was selected, in that patients with obstruction, abscess and fistulas generally were excluded. Nineteen patients had simple uncomplicated regional enteritis, 10 had extensive involvement of the ileum and jejunum, and six had ileocolitis.

The 14 patients with a good response have had no recurrence for from two to eight years. Since the response to medical treatment was satisfactory (good or fair) in 23 of the 26 patients in whom the follow-up was adequate, medical treatment appears to offer a great deal to many of these patients. However, this treatment would seem to be of most potential help in those patients with regional enteritis without complications.

SURGICAL TREATMENT

Sixty-five patients were operated upon. Operation was not advised for simple regional enteritis; the complications of the disease necessitated the operation in each case (table 5).

The indications for operation are grouped in table 5 according to the surgical procedures performed. From this table it is obvious that most patients with severe disease and complications including fistulas, abscesses and obstruction underwent resection. The presence of these serious complications did not prevent the surgeons from proceeding with resection. The

TABLE 5

Indications for Surgical Treatment

Indications	Incidence of Indications in Patients Who Underwent			Total Incidence of Indications
	Resection	Side-Tracking with Exclusion	Other Operations	
Obstruction	21	6	3	30
Fistulas	—	—	6	25
Internal	6	4	—	
External (RLQ)	8	1	—	
Anemia	3	1	5	9
Abscess	9	1	3	13
Perforation	1	0	—	1
Anal Fissure	0	2	—	2

extent of the disease and its complications must be considered when comparing the merits of resection with those of side-tracking with exclusion.

Follow-up studies of longer than one year were obtained in all but five of these 65 patients treated surgically (table 6). In 32 (53%) of those 60 patients the results were good, while in 14 (23%) the results were fair. Thus, results were satisfactory in 46 (76%) of the patients.

Meyers, Ruble and Ashley [1] reported satisfactory results after a long follow-up in 50 of 62 patients who underwent resections performed by various surgeons in a general hospital. The over-all results of operation for regional enteritis are encouraging, and do not support the current pessimistic attitude concerning treatment of the disease.

TABLE 6

Results of Operation in Regional Enteritis*

Operation	Result*			Dead†	Total
	Good	Fair	Poor		
Resection	20	3	4	1	28
Ileocolostomy with exclusion	7	5	2	0	14
Ileocolostomy without exclusion	1	4	2	0	7
Ileostomy	3	2	4	0	9
Entero-enterostomy	1	0	0	1	2
Total	32	14	12	2	60

* Please see text for definition of grades of results or response.

† The two deaths were not related to the enteritis. One patient had an argentaffinoma of the appendix and cecum with metastases, and the other had a carcinoma of the stomach involving the peritoneum.

A statistical comparison of the results of resection with those of any other procedure is not valid, due to the small sample. Because of the controversy concerning the comparative values of resection and of the side-tracking with exclusion procedure, we have made a general comparison (table 6); however, it is important to consider that many of the patients who underwent resection had more severe complications than did those who underwent an ileocolostomy with exclusion. After resection, good results were obtained in 20 (71%) and fair results in three (11%) of 28 patients who were traced; thus, results were satisfactory in 23 patients (82%). After ileocolostomy with exclusion, good results were obtained in seven (50%) and fair results in five (36%) of 14 patients who were traced; thus, results were satisfactory in 12 patients (86%).

Ileocolostomy without exclusion produced poor results: six of seven patients had recurrence (table 7). We believe that this operation should no longer be performed for regional enteritis.

TABLE 7

Recurrences After Operation in 60 Patients

Operation	No Recurrence, No. of Patients	Recurrence, No. of Patients			Total No. of Patients
		Medically Treated	Surgically Treated	Total	
Resection	13	9	6	15	28
Ileocolostomy					
with exclusion	4	6	4	10	14
without exclusion	1	2	4	6	7
Ileostomy	3	0	6	6	9
Entero-enterostomy	1	1	0	1	2
Total	22	18	20	38	60

Although the results of side-tracking procedure with exclusion were good, we prefer to have patients undergo resection. In general, it has become a surgical principle to remove disease when possible (appendicitis, ulcerative colitis, cholecystitis and peptic ulcer). For example, few cholecystostomies are performed today.

Postoperative Recurrence: Poor results of operation may be due to a recurrence of the disease, but the recurrence may be mild and may respond to further treatment, either medical or surgical. Meyers, Ruble and Ashley [1] observed that a recurrence of the disease after resection does not necessarily indicate a bad prognosis. Four of their seven patients who developed postoperative recurrences responded well to a second resection. Kiefer [20] reported that, of 42 patients who developed a postresection recurrence, 27 made satisfactory progress.

Since the location of the recurrence usually is at the site of the anastomosis and in the small intestine immediately proximal to the anastomosis (figure 1 A, B), the question arises as to whether all diseased tissue was removed at the first resection. The anastomosis should be made with small intestine that is normal both grossly and microscopically. It may be advisable to obtain specimens of the proximal line of resection for frozen section at the time of operation, to make certain that all pathologic tissue has been removed. Microscopic examination of frozen sections of the proximal line of resection has been done during operation in a number of our patients and has been a definite help. In several of our cases, small intestine that appeared grossly normal was found on frozen section examination to be involved, and further resection was done at the first operation.

The postoperative recurrence rate in our series was high (63% for the entire group). The rate was lowest (54%) in those patients who underwent resection, and highest (six of seven) in those who underwent ileocolostomy without exclusion.

In 29 of the 38 patients in whom the disease recurred, it did so within two years after operation; in 20 of those 29 patients it recurred within one

year after operation. In 18 of the 38 patients, recurrences were treated medically; the response was satisfactory in all 18. The remaining 20 patients underwent another operation—resection in 18, and ileocolostomy in

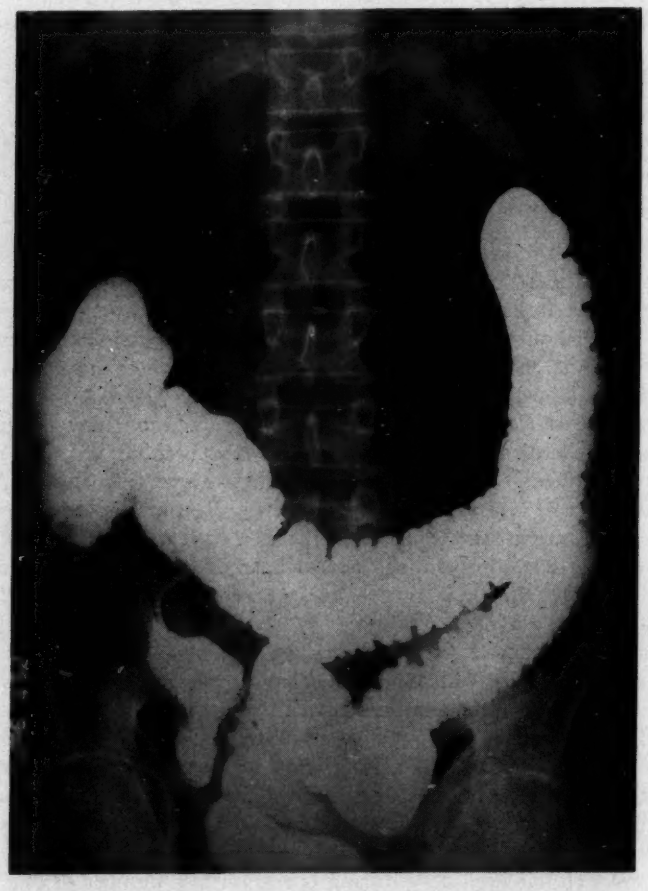

FIG. 1. A. Barium enema examination in 1956, showing typical recurrence of regional enteritis in the ileum just proximal to an ileocolostomy. Ileocolostomy had been performed in 1946, followed by resection of the terminal ileum in 1948. The patient showed evidence of recurrent enteritis in 1951. Yearly roentgen studies have revealed no progression of the enteritis since 1951. He has received minimal medical treatment and has been relatively asymptomatic.

two. There was an inadequate follow-up in two of these 20 patients, and one committed suicide after the second operation. In the remaining 17 patients the results of operation were good in five, fair in eight, and poor in four. Thus, the second operation produced satisfactory results in 13 patients.

In our series, as in those of others, postoperative recurrence of regional enteritis did not necessarily mean a poor prognosis. Thirty-one of our 36 patients in whom the disease recurred postoperatively and in whom the follow-up was adequate made satisfactory progress, either on medical treatment (18) or after a second operation (13).

FIG. 1. B. Spot films showing involvement of the ileum just proximal to the ileocolostomy. The involved ileum is narrowed, with some dilatation of the small bowel proximal to the involved area, indicating minimal partial obstruction. Despite these findings, the patient has been relatively asymptomatic on medical treatment for the last six years.

SUMMARY

Of 100 patients with regional enteritis who were seen at the Cleveland Clinic from 1946 through 1956, 35 received medical treatment alone and 65 underwent operation. The duration of follow-up was more than one year (average, 5.2 years) in 86 of these patients.

The medical treatment was supportive and nonspecific. Of the 35 patients treated medically, 23 had a satisfactory response, three an unsatisfactory response, and nine were traced for less than one year. The effects of specific facets of the medical program were difficult to establish, but apparently antibiotics (Terramycin in four and streptomycin in five patients) were beneficial; steroidal therapy was of help in five of 10 patients; and roentgen therapy was of value in three of six patients. From these findings we believe that medical therapy can be of benefit in patients with regional enteritis who have no severe surgical complications.

All of the 65 patients who underwent operation had complications of regional enteritis: obstruction in 30, fistulas in 25, abscesses in 13, and severe anemia or hemorrhage in nine. The indications for surgical treatment were the complications of the disease rather than the disease itself.

The results of operation were good in 32 patients, fair in 14 patients, and poor in 12 patients; five patients were followed less than one year, and two died from causes not related to the regional enteritis. Of the 28 patients who underwent resection and in whom the follow-up was adequate, 23 responded satisfactorily (good, 20 patients; fair, three patients).

The postoperative recurrence rate was high: 63% for the entire group, and 54% for the group that underwent resection. Of the 38 patients with postoperative recurrence, 18 were treated medically and 20 underwent another operation. Two of the 38 patients were lost to follow-up. Thirty-one of the remaining 36 patients responded satisfactorily to the further treatment.

We believe that the results of treatment in these 100 patients warrant an optimistic approach to the treatment of regional enteritis.

Summario in Interlingua

Cento patientes con enteritis regional esseva tractate al Clinica Cleveland inter 1946 e le fin de 1956. Un tractamento exclusivemente medical esseva usate in le casos de 35 patientes: 19 con le morbo in forma non-complicate e 16 con extense affectiones que faceva un operation contraindicate. Ex le 35 patientes qui esseva tractate medicalmente, 23 habeva un responsa satisfactori; in tres le responsa esseva non-satisfactori; e in nove le observation post-tractamental ha durate minus que un anno. Le effecto de specific drogas individual esseva difficile a evalutar, proque le majoritate del patientes recipeva therapias multiple, incluse dieta, supplementation de vitaminas, antispasmodicos, e altere mesuras general. Le agentes le plus benefic esseva le non-absorbibile sulfas, specialmente phthalylsulfathiazol (Sulfathaladina) e Azulfidina (Azopyrina). Micre doses de antibioticos in administration prolongate pareva esser de beneficio. Chloramphenicol (Chloromycetina) e Terramycina esseva usate in quatro patientes, e streptomycina—un vice per septimana como in tractar tuberculose—in cinque. Roentgenotherapia esseva usate in le casos de sex patientes e pareva beneficiar tres. Therapia a steroides in combination con non-absorbibile sulfas o in combination con antibioticos esseva empleate e continuate in octo casos. In cinque, le responsa esseva satisfactori. Plure patientes habeva remissiones de longe duration post le therapia a steroides.

Considerante que ex le 26 patientes a tractamento medical in qui le observation post-tractamental esseva adequate, 23 habeva un responsa satisfactori (bon o satis

bon), on debe concluder que le tractamento purmente medical ha multo a offerer a iste patientes.

Sexanta-cinque patientes esseva operate. Complicationes del morbo—i.e. obstruction, fistulas, abscessos—esseva considerate como indication pro le operation. Multes del patientes con le plus sever complicationes in qui le morbo esseva extense esseva subjicite a resectiones. Resultatos satisfactori esseva obtenite in 23 ex 28 resectiones (i.e. 82%). Isto include 20 con bon e 3 con satis bon resultatos. Post ileocolostomia con exclusion, bon resultatos o resultatos satisfactori esseva obtenite in 12 ex 14 patientes (i.e. 86%). Isto include septe con bon e cinque con satis bon resultatos. Ileocolostomia sin exclusion esseva effectuate in septe patientes e resultava in recurrentias in sex. Iste operation ha non essite executate a iste institution depost 1949, e nos opina que illo deberea esser abandonate como tractamento de enteritis regional. Le procentage del recurrentias post chirurgia esseva alte. Illo amontava a 63% pro le gruppo total sed solmente a 54% pro le patientes subjicite a resection. Tamen, ex 38 patientes con recurrentias post chirurgia, 31 respondeva satisfactorimente a un tractamento additional. Iste tractamento additional esseva medical in 18 e chirurgic in 20 casos.

Nos opina que le resultatos del tractamento de iste 100 patientes justifica un attitude de optimismo con respecto al problema therapeutic de enteritis regional. Multo pote esser facite per medio del tractamento medical. Quando complicationes se disveloppa, intervention chirurgic in tal patientes es indicate e offere le promissa de esser de beneficio.

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HEPATIC DYSFUNCTION DUE TO CHLORPROMAZINE HYPERSENSITIVITY *

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The complete pathogenesis of jaundice due to chlorpromazine is obscure, but a number of facts have become known.

Approximately 1% of people treated with chlorpromazine for two or more weeks have developed clinical jaundice.[1] Its appearance has first been noted 10 to 31 days after the initiation of drug therapy,[2, 3, 4] and as long as 18 days after withdrawal of the drug.[2, 5, 6] Its incidence and severity have not been influenced by age, sex, size of daily dose or duration of drug therapy before icterus. It has occurred after as little as 50 to 75 mg. taken for one day.[5, 7]

After the appearance of icterus the results of liver function tests have been consistent with incomplete obstructive jaundice, and liver biopsies have shown intrahepatic cholestasis, with or without an inflammatory component in the portal spaces, and little or no evidence of parenchymal injury.[1, 2, 3, 4, 8, 9, 10, 11, 12]

After chlorpromazine has been withdrawn, jaundice usually has subsided within weeks, but sometimes has lasted for months.[13] After recovery, re-administration of the drug may not cause recurrence of jaundice.[14, 15, 16]

In two cases, jaundice disappeared during the continued administration of chlorpromazine.[17]

Few data are available on the hepatic state preceding jaundice.[18, 19] One significant report is based on liver function tests done periodically in 50 patients receiving chlorpromazine for from one to seven weeks.[19] Twenty-one developed hepatic dysfunction, anicteric in all but two. In 13, dysfunction subsided although drug therapy was uninterruptedly maintained. In the remainder, medication was stopped. The most frequent laboratory abnormalities were increases of bromsulfalein retention and serum alkaline phosphatase.

There have been a few isolated case reports of hepatic dysfunction recurring after the re-administration of chlorpromazine.[1, 6, 7, 19] There was laboratory evidence of dysfunction as early as from five to 36 hours after the first dose. In two of these cases there was recurrence despite the concurrent employment of cortisone in one,[6] and ACTH with cortisone in the other.[1]

There has been a recent brief reference to unpublished data about

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jaundice recurring in nine of 11 recovered patients to whom the drug had been re-administered.[20]

To explore further the nature and pathogenesis of the hepatic reaction to chlorpromazine, the following studies were undertaken.

Study I

Method: Chlorpromazine was administered daily for a minimal period of one month to hospitalized psychotic patients who had not previously received the drug. Over a period of four and one-half months there became available for study 68 patients who had been hospitalized for from two days to three years. All but two were males. Ages ranged from 21 to 71 years, with a median age of 36.

Throughout the investigative period these patients received no other drugs, remained adequately hydrated and nourished, and developed no acute illness or fever. There was no exposure to any hepatotoxic agent and, except for a case of homologous serum hepatitis two years before, there had been no overt case of viral hepatitis at this hospital for four years.

The minimal investigative period of one month was selected because, of more than 1,800 psychiatric patients at the Brockton Veterans Administration Hospital who received chlorpromazine daily for one month or longer, the 19 who developed icteric or anicteric hepatic dysfunction did so within a month of beginning drug therapy.

Just before the initiation of treatment, the following laboratory tests were performed in each case and were repeated every Monday and Wednesday during the first month of treatment or longer: cephalin flocculation (normal, — to +), thymol turbidity (normal, 0–5 units), zinc turbidity (normal, 0–8 units), bromsulfalein retention (normal, $< 4\%$ in 45 minutes), serum glutamic oxalacetic transaminase (normal, 8–40 units),[21] serum alkaline phosphatase (normal, 1–4 Bodansky units), serum total bilirubin (normal, to 1.2 mg. total), prompt direct-reacting bilirubin, urinary bile, urinary urobilinogen (dilution method: normal, 1:20), white cell count and differential.

Chlorpromazine was orally administered in divided doses. Each patient's daily dosage was maintained or increased throughout the investigative period. The daily dosage for all individuals within the group ranged from 75 to 1,200 mg., with a median of 461 mg.

Prior to treatment, 50 of the 68 patients had completely normal liver function tests. These comprised the "Normal Liver Group."

Bromsulfalein retention was increased (8% to 19.5%) in the remaining 18, of whom three had a positive cephalin flocculation (2+ to 3+) or thymol turbidity (8.8 units). One had a serum transaminase of 204 units due to an acute exacerbation of alcoholic cirrhosis. These comprised the "Abnormal Liver Group."

TABLE 1

Occurrence of Abnormalities of Liver Function Tests in Patients during One Month of Chlorpromazine Therapy

Abnormalities*	Number of Patients
None	19
BSP	15
BSP and Trans.	6
BSP, Trans. and APh	5
Trans.	4
BSP, Trans., APh, SB, TT and UU	1

* BSP = Bromsulfalein retention.
Trans. = Serum transaminase.
APh = Serum alkaline phosphatase.
SB = Serum total bilirubin.
TT = Thymol turbidity.
UU = Urinary urobilinogen.

Results: Normal Liver Group: During the month of treatment 19 patients maintained completely normal liver function, but 31 patients, though asymptomatic, developed abnormal values of one or several liver function tests (table 1).

Bromsulfalein retention was increased most frequently, serum transaminase less often, and serum alkaline phosphatase occasionally. In only two cases were there elevations of serum total bilirubin—1.4 mg. to 3.1 mg. (table 3, case 5; table 6). Thymol turbidity rose in one case to 10 units (table 6). Cephalin flocculation and zinc turbidity remained normal.

Neither age nor dosage level bore a significant statistical relationship to the incidence, time of occurrence, or degree of hepatic reaction.

Except for a persistent, slightly increased bromsulfalein retention in one

TABLE 2

Increased Bromsulfalein Retention in 27 Patients

Time of Appearance after Beginning Chlorpromazine	Number of Patients	
1–3 days	0	
4–7 days	8	
2nd week	14	
3rd week	4	
4th week	1	
% of Dye Retained		
6	5	66%
7–10	13	93%
11–15	7	
23	1	
40	1	
Duration, in Days, of Increased Dye Retention		
<7	12	
7–13	6	
14–28	6	
>28	3	

patient who refused further study after eight weeks (table 3, case 2), all abnormalities of liver function tests spontaneously disappeared during the uninterrupted continuance of chlorpromazine therapy.

Increased Bromsulfalein Retention: Increased retention of bromsulfalein developed in 27 patients. In 15 of them this was the sole abnormality (table 3). In the remaining 12 there was also an elevation of serum transaminase, with or without an accompanying elevation of serum alkaline phosphatase (tables 4, 5 and 6).

TABLE 3

Increased Bromsulfalein Retention as the Sole Abnormality*

	Weeks	1		2		3		4		5		6	8	10	15	19
Cases	BSP	N	N	N	N	6.5	9.5	6.5	7.5	6	8.5	9.5		7.5	7.5	N
1	SB	.5	.5	.3	.3	.5	.2	.3	.5	.6	.5	.7		1.1	.8	.5
	BSP	N	8.5	8.5	9.8	10	9.5	7.5	6.5				8			
2	SB	.6	1.2	.5	.8	.3	.5	.6	.6							
	BSP	N	7.5	7.5	5	6.5	N	7.5	N							
3	SB	.5	.9	.8	.6	.3	.5	.5	.5							
	BSP	N	N	N	8.5	23	7.5	N	N							
4	SB	.8	.3	.8	.5	.7	.8	.8	.5							
	BSP	N	N	8.5	8	N	N	N	N							
5	SB	.6	.6	1.4	.9	.4	.6	.6	.5							
	BSP	N	N	6.5	N	12.5	N	N	N							
6	SB	.3	.6	.5	.8	.6	.3	.7								
	BSP	N	9	N	N	N	N	N	N							
7	SB	.3	.5	.6	.3	.2	.3	.3	.3							
	BSP	N	6	N	N	N	N	N	N							
8	SB	.8	.9	.5	.5	1.2	.5	.8	.5							
	BSP	N	10	N	N	N	N	N	N							
9	SB	.5	.3	.5	.3	.5	.5	.5	.5							
	BSP	N	N	6	N	N	N	N	N							
10	SB	.9	.3	1	.5	.2	.5	.4	.5							
	BSP	N	N	6.5	N	N	N	N	N							
11	SB	.5	.8	.7	.5	.9	.3	.8	.3							
	BSP	N	N	N	N	6	N	N	N							
12	SB	.3	.5	.2	.6	.8	.3	.2	.3							
	BSP	N	N	N	N	7.5	N	N	N							
13	SB	.6	.5	.6	.5	.2	.2									
	BSP	N	N	N	N	N	7	N	N							
14	SB	.3	.5	.6	.5	.5	.5	.3	.7							
	BSP	N	N	N	N	N	N	N	9	N	N					
15	SB	.6	.6	.3	.5	.3	.5	.6	.5	.5	.5					

* N = Normal.

In 22 cases increased retention appeared within from four to 14 days of initiation of drug therapy. In the remaining five cases increased retention appeared during the third or fourth week. The abnormal degree of retention ranged from 6% to 40%. In 18 cases the duration of abnormal retention was less than two weeks; in six it was two to four weeks, and in three, longer than four weeks (table 2). There was no correlation between the degree and the duration of increased bromsulfalein retention. There was also no correlation between the degree or the duration of increased retention and the occurrence of abnormalities of the other liver function tests.

TABLE 4

Associated Increases of Bromsulfalein Retention, Serum Alkaline Phosphatase and Serum Transaminase

	Weeks	1		2		3		4		7
Cases	BSP	N	12.5	7	N	N	N	N	N	
1	APh	N	6	4.6	4.6	N	N	N	N	
	Trans.	N	N	83	N	N	N	N	N	
	SB	.5	.5	.6	.5	.5	.8	.3	.5	
	BSP	N	N	12.5		10.8	N	N	N	
2	APh	N	N	10.3		8	4.8	5.3	N	
	Trans.	N	N	200		78	N	N	N	
	SB	.5	.5	.8		.5	.6	.5	.8	
	BSP	N	N	10	N	N	N	N	N	
3	APh	N	N	6	6	N	N	N	N	
	Trans.	N	N	79	N	N	N	N	N	
	SB	.7	.6	.6	.5	.7	.7	.5	.5	
	BSP	N	N		12	5	N	N	N	
4	APh	N	N	N	5	N	N	N	N	
	Trans.	N	N	96	65	N	N	N	N	
	SB	.6	.6	1	.6	.8	.3	.5	.6	
	BSP	N	N	9	9.5	6	5	7	6	N
5	APh	N	N	5.7	5	5.2	6.2	7.2	5.2	N
	Trans.	N	N	83	54	N	N	N	N	N
	SB	.8	.6	.8	.7	.9	.5	.6	.8	.5

TABLE 5

Associated Increases of Bromsulfalein Retention and Serum Transaminase

	Weeks	1		2		3		4		5		6		7	28
Cases	BSP	N	N	N	N	N	6.5	N	N						
1	Trans.	N	N		N	52	49	N	N						
	SB	.9	.5	.3	.5	.5	1.2	.6	.3						
	BSP	N	N	6	N	N	N	6	6						N
2	Trans.	N	N	62	81	110	120	96	68						N
	SB	.8	.3	.5	.3	.5	.5	.5	.6						
	BSP	N	14.5	11	12.5	9	6.5	6.5	7	8.8	N	6.5	N	N	
3	Trans.	N	55	64	55	N	N	N	N	N	N	N	N	N	
	SB	1.1	.5	.5	.5	.7	.6	.5	.8	1.2	.6	.9	.8	.5	
	BSP	N	N	6	8	7	N	N	N						
4	Trans.	N	N	80	76	68	N	N	N						
	SB	.5	.5	.3	.6	.5	.5	.5	.1						
	BSP	N	N	N	N	6	N	N	N						
5	Trans.	N	N	N	N	93	N	N	N						
	SB	.5	.5	.5	.5	.7	.5	.5	.5						
	BSP	N	6.5	N	12.5	N	N	N	N						
6	Trans.	N	N	49	N	N	N	N	N						
	SB	.5	.7	.5	.6	1	.7	.6	.5						

TABLE 6

Development and Subsidence of Icteric Hepatic Dysfunction during Uninterrupted Administration of Chlorpromazine

Weeks	1		2		3		4		5		6		7		12
Total SB	1	.3	3.1	1.4	2.2	2.8	2.2	1.8	.5	.8	.9	.7	.1	.3	.7
Direct SB	.6	.2	1.8	.9	2.0	2.4	1.6	1.3	.4						
BSP	N	N	21	12.5	18.5	40	26	12	N	N	N	N	N	N	N
Trans.	N	N	N	N	52	61	66	54	N	N	N	N	N	N	N
APh	N	N	4.5	5	4	13	13	15	10	10	7	6	4.5	4.8	N
TT	N	N	N	N	N	N	5	N	10	6	6	N	N	N	N
Urine Bile	0	0	±	0	+		0	0	0	0					
UU	N	N	1:400	1:200	1:100		1:300	1:100	N	N					
Eos., %	N	N	6	8	24	25	N	N	N	N	N	N	N	N	N

Elevated Serum Transaminase: In 16 patients serum transaminase was elevated, ranging from 49 to 200 units. Except for one instance of a rise during the first week, serum transaminase rose to abnormal levels during the second or third week of chlorpromazine therapy.

In seven patients, serum transaminase returned to normal levels within one week; in eight, within two to three weeks, and in one it remained elevated for more than three weeks.

In 12 of these 16 patients the elevated serum transaminase was always concurrent with increased bromsulfalein retention, and in six of these 12 it was also associated with increased serum alkaline phosphatase (tables 4, 5 and 6). In the remaining four patients an elevated serum transaminase was the sole abnormality, with levels of 50 to 70 units remaining elevated for from seven to 12 days.

In five of six patients with associated abnormal increases of only bromsulfalein retention and serum transaminase, their rise and subsequent fall to normal levels coincided closely. In the sixth, increased bromsulfalein retention persisted for more than two weeks after serum transaminase had returned to normal.

In four of six patients with associated abnormal levels of bromsulfalein retention, serum alkaline phosphatase and serum transaminase, there was a closely concurrent rise and fall. In the two other patients, increased serum alkaline phosphatase persisted after the other tests had returned to normal (table 4, case 2; table 6).

Serum alkaline phosphatase was less than 10 Bodansky units in all but one case (table 6).

In two cases there were elevations of serum total bilirubin. In one of them there was an associated bromsulfalein retention of 8.5% (table 3, case 5). In the other there were accompanying abnormal values of several hepatic function tests (table 6). All abnormalities disappeared while chlorpromazine therapy was continued and the daily dosage increased from 400 mg. to 800 mg. There were no symptoms or fever. Medication has been

continuously administered to the present (a total of six months) without evidence of recurrent hepatic dysfunction.

Results: Abnormal Liver Group: During the month of chlorpromazine therapy, three patients developed a further increase of dye retention, increased serum alkaline phosphatase and serum transaminase similar in degree to the abnormal values found in the Normal Liver Group. All of these acute abnormalities of liver function disappeared during the continuous administration of chlorpromazine.

At the end of one month four patients displayed normal liver functions and 14 showed no change.

Eosinophilia: Of the 34 patients who did not develop acute abnormalities of liver function, 17 (50%) manifested eosinophilia of from 5 to 14% at some time during the first month of drug therapy.

Of the 34 who developed acute abnormalities of liver function, 24 (78%) manifested eosinophilia, with only two exceeding 15% (17% and 25%). In seven of the 24, eosinophilia preceded or followed but did not accompany the phase of hepatic dysfunction.

Study II

Method: To 10 hospitalized patients completely recovered from icteric or anicteric hepatic dysfunction due to chlorpromazine, the drug was orally re-administered daily for periods ranging from one day to more than two months. Except for oral synthetic adrenal cortical hormone to four of these patients, no other medications were given. All patients were closely studied for the development of abnormal liver function.

Results: In four no abnormalities of liver function occurred, and drug administration has been maintained for from one to three years without evidence of hepatic dysfunction. Hepatic dysfunction rapidly ensued in six. Their case abstracts, plus one related abstract, follow.

Case Reports

Case 1. This patient was a 33 year old male. Thirteen days after he had been started on chlorpromazine, 100 mg. daily, headache, fever and bilirubinuria occurred. Serum total bilirubin was 3.5 mg., two-hour urinary urobilinogen was 2.5 Ehrlich units (normal, 0.3 to 1.5 E.U.). Drug therapy was stopped.

Three months after laboratory evidence of complete hepatic recovery, chlorpromazine, 150 mg., was readministered daily. Three days later general malaise occurred. Serum total bilirubin was 4.6 mg. Drug therapy was stopped.

Five weeks after laboratory evidence of complete hepatic recovery, chlorpromazine, 150 mg., was re-administered in doses of 50 mg. for one day. After the second dose mild abdominal pain occurred. The next day the serum total bilirubin was 1 mg.; bromsulfalein retention, 14.5%. Drug therapy was stopped.

Case 2. This patient was a 31 year old female. Eight days after she had been started on chlorpromazine, 400 mg. daily, headache and malaise occurred. Serum total bilirubin was 1.3 mg.; bromsulfalein retention, 16%. Drug therapy was stopped.

Two months after laboratory evidence of complete hepatic recovery, chlorpromazine, mg. 75, was re-administered daily. Forty-eight hours after the first dose, malaise and bilirubinuria occurred. Serum total bilirubin was 1.6 mg., bromsulfalein retention was 25%, and urinary urobilinogen was 1:40. Drug therapy was stopped.

Case 3. This patient was a 26 year old male. Eight days after he had been started on chlorpromazine, 300 mg. daily, vomiting and fever occurred. Drug therapy was stopped. Daily vomiting or regurgitation persisted. One week after drug therapy had been stopped, generalized abdominal pain and fever (104.2° F. rectal) occurred. Three days later icterus was noted. Serum total bilirubin was 3.8 mg.

Two months after laboratory evidence of complete hepatic recovery, cortisone, 100 mg. daily, was begun. Chlorpromazine, 25 mg., was re-administered next day, and 300 mg. on the day following. Within 24 hours after the first dose, vomiting occurred and the temperature rose to 103° F. Serum total bilirubin was 4.6 mg.; serum transaminase, 192 units.[6]

Case 4. This patient was a 65 year old male. Eight days after he had been started on a single nightly dose of chlorpromazine, 50 mg., a generalized erythematous maculopapular eruption occurred. Drug therapy was stopped. Serum total bilirubin was 0.9 mg.; bromsulfalein retention, 18.5%; serum alkaline phosphatase, 5.9 Bodansky units; serum transaminase, 58 units. Forty-eight hours later, serum total bilirubin was 0.5 mg.; bromsulfalein retention, 29%; serum alkaline phosphatase, 14.4 Bodansky units; serum transaminase, 130 units.

Six weeks after complete recovery, chlorpromazine, 25 mg., was re-administered daily for three days. Forty-eight hours after the first dose, serum total bilirubin was 0.5 mg.; bromsulfalein retention, 20%; serum alkaline phosphatase, 5 Bodansky units; serum transaminase, 103 units. Ninety-six hours after the first dose the serum total bilirubin was 1 mg.; bromsulfalein retention, 36%; serum alkaline phosphatase, 13 Bodansky units; serum transaminase, 176 units. There were no symptoms or fever.

Two weeks after recovery, prednisone, 20 mg. every eight hours, was begun. Next day, chlorpromazine, 25 mg. daily, was re-administered. Forty-eight hours after the first dose of chlorpromazine, serum total bilirubin had risen from 0.3 mg. to 0.9 mg., bromsulfalein retention was 18.5%, and serum alkaline phosphatase was 4 Bodansky units. There were no symptoms or fever.

Case 5. This patient was a 66 year old male. Sixteen days after he had been started on chlorpromazine, 150 mg. daily, asymptomatic jaundice was noted. Serum total bilirubin was 5.5 mg.; serum transaminase, 120 units. Drug therapy was stopped. Recovery occurred after three months. Two and one-half months after recovery a single dose of chlorpromazine, 25 mg., was re-administered. Twenty-four hours later, serum total bilirubin was 1.3 mg.; bromsulfalein retention, 41%; serum transaminase, 148 units; serum alkaline phosphatase, 2.2 Bodansky units; two-hour urinary urobilinogen, 2.8 Ehrlich units. There were no symptoms or fever.

Two weeks after recovery, prednisone, 20 mg. every eight hours, was begun. Next day, chlorpromazine, 25 mg. daily, was re-administered. Twenty-four hours after the first dose of chlorpromazine, serum total bilirubin had risen from 0.5 mg. to 1.5 mg., bromsulfalein retention was 51%, and serum alkaline phosphatase was 2.7 Bodansky units. There were no symptoms or fever.

Case 6. This patient was a 38 year old male. Twenty-one days after he had been started on chlorpromazine, 200 mg. daily, asymptomatic jaundice was noted. Serum total bilirubin was 9 mg. Recovery occurred after four months. Five months after recovery, cortisone, 50 mg. every six hours, was begun. Next day chlorpromazine, 150 mg. daily, was re-administered. Forty-eight hours after the first dose of chlorpromazine, serum total bilirubin was 1.1 mg.; bromsulfalein reten-

tion, 18.5%; two-hour urinary urobilinogen, 2.5 Ehrlich units. There were no symptoms or fever.

Case 7. This patient was a 41 year old male. Chlorpromazine, 50 mg. three times daily, had been prescribed. Ten hours after ingesting the first dose the patient was awakened by crampy abdominal pain, headache, generalized muscular aching, and an oral temperature of 101° F. Two more doses of chlorpromazine were taken. Thirty-six hours after the first dose, serum total bilirubin was 1.9 mg.; bromsulfalein retention, 20% (patient afebrile); serum transaminase, 111 units; bilirubinuria, trace. Within four days the white cell count had risen to 25,000 with an eosinophilia of 16%.

The patient volunteered that his symptoms were identical to those experienced *three years before,* when he had received a "new drug" at another hospital. Examination of that hospital's record disclosed that after having ingested chlorpromazine, 150 mg. daily for eight days, he had developed chilliness, headache, generalized muscular aching, crampy midabdominal pain, and a temperature of 102° F. Cephalin flocculation, serum total bilirubin and serum alkaline phosphatase were examined once and found normal. The bromsulfalein dye test was not performed.

During or following a bout of jaundice due to chlorpromazine, each of 15 patients was injected intradermally with 0.1 c.c. serum drawn from a patient ingesting chlorpromazine, 1,000 mg. daily. The skin tests were negative at one hour and at 24 hours.

Discussion

Asymptomatic hepatic dysfunction, anicteric in all but two cases, occurred in 34 of 68 patients receiving chlorpromazine for one month. The dysfunction disappeared during continued and uninterrupted administration of the drug.

Increased bromsulfalein retention, reflecting impairment of hepatocellular function, was the most frequent manifestation of the early hepatic reaction to chlorpromazine, and appeared as early as four days after drug therapy was begun.

Less frequent was an abnormal rise of serum transaminase, reflecting acute liver cell injury.[21] Small rises in serum transaminase sometimes occurred as the only evidence of hepatic dysfunction, and this probably reflected liver cell injury insufficiently extensive to cause increased bromsulfalein retention.

In seven cases of frank jaundice due to chlorpromazine (serum total bilirubin, 3.1 mg. to 10 mg.), serial transaminase levels rose no higher than they did in the anicteric hepatic reactions described in this study (to 200 units).[22] This contrasts with the marked elevations found in icteric viral hepatitis.[21, 23]

Serum alkaline phosphatase rose only (but not always) when both dye retention and serum transaminase increased.

In five of six cases, abnormal values of all three tests appeared concurrently, with no associated rise of serum total bilirubin or of the prompt direct-reacting fraction.

In the absence of hyperbilirubinemia, elevated serum alkaline phosphatase

may be related to hepatocellular impairment and injury, or it may be the result of an intrahepatic biliary obstructive process insufficient in degree to cause a rise of serum bilirubin.[24] It might be the result of both hepatocellular and biliary factors, especially in the icteric phase.

The reported results of liver function tests, performed after the appearance of jaundice, have seemed to be consistent with a purely obstructive process. Serum total bilirubin has been increased, with the prompt direct-reacting fraction predominant. The serum alkaline phosphatase and serum cholesterol have usually been increased. In my own cases[22] they were elevated with equal frequency (70%), but both were not always elevated in the same case. The cephalin flocculation and thymol turbidity have usually been negative, but infrequently they have become positive.[4, 11, 13, 22]

Urine urobilinogen excretion has been reported as normal or low. However, I have frequently found the two-hour urinary urobilinogen excretion to be increased, reflecting impaired hepatocellular function. In 13 cases of jaundice due to chlorpromazine, serial determinations of two-hour urinary urobilinogen excretion revealed normal or increased values in all but one throughout the icteric phase. It was found to be increased for part or all of this phase in nine of the cases—when serum total bilirubin was rising (in one case, at 0.8 mg.%), at peak level (maximal in this group, 11 mg.%), subsiding, and after reaching normal values.[6, 22]

After the appearance of jaundice the hepatocellular origin of an elevated serum transaminase would be obscured, since comparable elevations are found in some cases of extrahepatic obstructive jaundice.[18]

No liver biopsy has been obtained during the anicteric phase of hepatic reaction to chlorpromazine, but many biopsies have been obtained during the icteric phase. The main feature common to all is a varying degree of bile stasis in the centrolobular bile canaliculi. There are usually deposits of brownish pigment in neighboring parenchymal and Kupffer's cells. Parenchymal involvement is minimal or undemonstrable. Occasionally some central hepatic cells show slight focal degenerative changes. The portal areas appear normal or are slightly infiltrated with neutrophils, lymphocytes, mononuclear cells, and sometimes eosinophils.

Whether this picture of intrahepatic cholestasis and the accompanying clinical findings is due solely to a primary impairment of hepatocellular metabolism that somehow disturbs the mechanism of normal bile formation or transport, or is due partly to a concurrent disturbance of the finer biliary passages, with the ultimate production of regurgitation, bile stasis and intrahepatic biliary obstruction, must await further investigation.

It does appear, however, that the underlying mechanism of the hepatic disturbance is one of drug hypersensitivity.

The onset of hepatic dysfunction four or more days after initial internal contact with chlorpromazine; the subsidence, in some cases, of the hepatic reaction during continued drug administration; the failure of dysfunction

to recur, in other cases, upon re-administration of chlorpromazine; and, in others, the accelerated recurrence of dysfunction upon readministration of the drug—all these phenomena have been precisely duplicated by the behavior of allergic reactions caused by sulfonamides and penicillin.[25, 26]

The administration of moderate and large doses of synthetic adrenal cortical hormone has failed to suppress the re-appearance of hepatic manifestations of chlorpromazine hypersensitivity. The influence of the hormone upon the subsequent course of recurrent hepatic dysfunction is presently being investigated.

On the basis of the data presented in this report, it appears that approximately 50% of people receiving chlorpromazine for one month may develop a hypersensitivity to the drug manifested by a mild, subclinical, asymptomatic hepatocellular dysfunction from which they recover spontaneously while drug administration is continued; and that approximately 1% may progress to clinical jaundice, from which some may spontaneously recover while the drug continues to be uninterruptedly administered, and some—having recovered after withdrawal of the drug—may later tolerate it without again incurring hepatic dysfunction.

These facts should not be taken as encouragement of casualness toward chlorpromazine-induced jaundice. One cannot predict whether this dysfunction might become increasingly severe under continued drug therapy, or eventually subside. Therefore, at the first evidence of jaundice or symptomatic anicteric hepatic dysfunction, chlorpromazine should be stopped, except in relevant, rigorously supervised research problems. After complete hepatic recovery the drug may be re-administered if desired, but with determinations of bromsulfalein retention every other day during the first week of treatment. If hepatic dysfunction becomes evident, the drug should be stopped.

Summary and Conclusions

Asymptomatic hepatic dysfunction occurred in 34 of 68 patients during the first month of chlorpromazine therapy. In 32 the dysfunction was anicteric. In the 34 patients normal hepatic function spontaneously returned during the continued administration of the drug.

The earliest phase of hepatic reaction to chlorpromazine is hepatocellular impairment and injury. The most reliable indicator of this phase is the bromsulfalein excretion test.

Six of 10 other cases, completely recovered from icteric or anicteric hepatic dysfunction, underwent rapid recurrence of dysfunction upon re-administration of chlorpromazine.

Hepatic dysfunction caused by chlorpromazine appears to be based primarily upon drug hypersensitivity. Synthetic adrenal cortical hormone, concurrently administered with chlorpromazine, did not prevent recurrence of hepatic dysfunction.

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SUMMARIO IN INTERLINGUA

Esseva executate duo studios pro explorar le natura e le pathogenese del reaction hepatic a chlorpromazina.

In le prime del studios, chlorpromazina esseva administrate un mense o plus a 68 patientes hospitalisate. Le etates del patientes variava inter 21 e 71 annos. Le dosages diurne variava inter 75 e 1.200 mg.

Multiple tests del function hepatic esseva effectuate ante le initiation del tractamento e postea duo vices per septimana durante un mense o plus.

Intra le prime mense, 34 patientes disveloppava transiente, asymptomatic, subclinic dysfunction hepatic que subsideva spontaneemente in le curso del non-interrumpite administration del droga. Ni le etate del patiente, ni le magnitude del dose administrate manifestava ulle relation al incidentia, al tempore del occurrentia, o al grado del reaction hepatic.

Augmento del retention de bromsulfaleina (6% a 40%) esseva le plus frequente signo precoce de reaction hepatic. Le retardo minime de su apparition a partir del comenciamento del therapia esseva quatro dies. Minus frequente esseva un elevation del nivello de transaminase seral (49 a 200 unitates) e, in casos sporadic, un elevation del nivello de phosphatase alcalin del sero (5 a 15 unitates de Bodansky).

In le secunde studio, chlorpromazina esseva re-administrate diurnemente a 10 patientes qui se habeva completemente restablite ab anicteric o icteric dysfunction hepatic que habeva essite causate per chlorpromazina.

Quatro del patientes manteneva un normal function hepatic durante un a tres annos de administration quotidian del droga.

Sex del patientes manifestava anicteric o icteric dysfunction hepatic intra 48 horas post le initiation del tractamento. Synthetic hormon adrenocortical, administrate a quatro del sex al mesme tempore como le chlorpromazina, non succedeva a prevenir le recurrentia de dysfunction hepatic.

Es formulate le conclusiones (1) que le subjacente mechanismo de dysfunction hepatic in consequentia de chlorpromazina pertine al dominio del hypersensibilitates drogal, (2) que le plus precoce phase del reaction hepatic a chlorpromazina es damnification e injuria hepatocellular, e (3) que le indice le plus fidel de iste phase es le test de excretion de bromsulfaleina.

Es discutite le question si le disturbation hepatic resulta exclusivemente de un damnification primari del metabolismo hepatocellular que disturba in un maniera o un altere le mechanismo del formation o del transporto normal de bile o si illo resulta in parte de un disturbation concurrente de fin passages biliari, con—ultimemente—le consequente production de regurgitation, stase biliari, e intrahepatic obstruction biliari.

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DIABETIC NEUROPATHY PRESENTING AS THE INITIAL CLINICAL MANIFESTATION OF DIABETES*

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NEUROPATHY occurring in association with diabetes mellitus presents many obscure features. The etiology, pathology and therapy are essentially unknown, and the diagnosis itself is one of exclusion and beset with many pitfalls.[1] One of the few areas in this perplexing field that has won wide acceptance by many leading authorities is that the neuropathy follows a prolonged period of poor diabetic control.[2-6] This view, however, is inconsistent with recorded observations of neuropathy actually preceding or accompanying the onset of any clinical manifestations of diabetes.

Diabetic neuropathy antedating the clinical appearance of diabetes mellitus has been recorded, frequently as an incidental finding in surveys of relatively large numbers of patients with this syndrome. Jordan [7, 8] described a patient who had neuritis 12 years before the presence of diabetes was clinically evident; he also noted four patients whose neuritic symptoms preceded diabetes, and seven others with simultaneous onset of the two conditions. Similar findings were mentioned by several other authors,[9-14] including a case of ocular motor paralysis.[15]

It is the purpose of this presentation (1) to illustrate by documented case material that neuropathy may be the initial clinical manifestation of diabetes, and (2) to indicate the important implications of this observation from both practical and theoretic aspects.

CASE REPORTS

Case 1. This 32 year old housewife had been entirely well until four weeks before, when she became aware of a painful pulling sensation behind the left eye. The upper lid was swollen, but there was no lacrimation or conjunctivitis. She denied diplopia, but had difficulty in looking to the left and upwards. The swelling gradually subsided but the visual difficulty persisted. One week later she began to have moderately severe bifrontal headaches, which were constant and were uninfluenced by position, activity or mild analgesics. Concomitantly, she developed nausea and anorexia but did not vomit. There were no signs or symptoms indicative of uncontrolled glycosuria.

Past history and systemic review were unremarkable except for the presence of obesity for many years. There was no history of polyuria, polydipsia or weight loss. The gynecologic history revealed that the first pregnancy resulted in a miscarriage at six months, the second yielded a stillbirth with congenital cranial defect, and the third

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and fourth pregnancies produced two normal children each weighing seven and a half pounds. The family history revealed that the father and two paternal aunts had diabetes mellitus.

Physical examination showed a well developed, obese young female weighing 194 pounds. Heart and lungs were normal; blood pressure was 120/80 mm. of Hg. The abnormal findings were confined to the neurologic and ophthalmologic examinations. The neurologic examination revealed the sensorium to be clear; visual fields, normal; ocular movements, normal except for weakness of the left superior rectus. The pupils were normal; there was slight ptosis of the left eye lid; there was no nystagmus. The rest of the neurologic examination, including motor and sensory investigation, was entirely normal. Ophthalmologic consultation corroborated the findings of ptosis of the left eyelid, with weakness of the medial, inferior, oblique and superior rectus. Pupils and fundi were normal. Visual fields and acuity were normal.

Laboratory examination revealed hemoglobin, 12.5 gm.%; hematocrit, 41%; white blood count, 7,200 per cubic millimeter, with a normal differential. Urine: specific gravity, 1.030; albumin and sugar, negative. Blood serology in test for syphilis, negative. An electrocardiogram was normal. X-ray examinations of the skull, orbits and optic foramina were normal. Radioactive iodine uptake was 50% in 24 hours. An electroencephalogram was normal.

Course: The only neurologic abnormality detected was the partial third nerve palsy. To exclude the possibility of internal carotid artery aneurysm, arteriography was performed. This was normal. A Tensilon test was negative. Because of the transient oculomotor palsy, the striking family history of diabetes and negative arteriography, the possibility of diabetes was strongly suspected, even though there was no glycosuria. A glucose tolerance test was therefore performed.

Time	Urine Sugar	Blood Sugar
Fasting	0	163 mg.%
½ hour	0	213 mg.%
1 hour	3 plus	246 mg.%
2 hour	3 plus	226 mg.%
3 hour	0	168 mg.%

This established the diagnosis of diabetes. Under observation and without specific therapy, except an incidental attempt to induce necessary weight loss, the eye symptoms as well as the headaches cleared rapidly and completely, so that within two months after the onset the patient was perfectly normal. The diabetes has since been kept under excellent control by simple dietary measures, without the use of insulin or other hypoglycemic agents.

Comment: The nature of onset, the type of isolated optic nerve palsy, the absence of accompanying neurologic phenomena and the benign course with spontaneous recovery are entirely consistent with diabetic neuropathy involving the external ocular muscles. This, in association with the strong family history, led to the performance of a glucose tolerance test, which was typically diabetic. The relative youth of this patient speaks against any "preëxistent prolonged period of unrecognized and controlled hyperglycemia and glycosuria." On the contrary, one would normally anticipate a classic onset of diabetes in this age group, with polyuria, polydipsia, polyphagia, etc., which were completely lacking.

Case 2. This 60 year old white male, 11 months before, had developed severe, constant pain in both lower extremities, radiating down the anterior surfaces of both thighs and legs, much more severe on the left. The pain was not related to exertion

and was not relieved by heat; it was worse at night. Eight months later he developed the syndrome of diabetes mellitus, characterized by polyuria, polydipsia, nocturia, weight loss of 14 pounds, hyperglycemia (fasting blood sugar, 328 mg.%) 4 plus glycosuria, and severe pruritus of both legs. He was started on therapy consisting of diet and protamine zinc insulin, 24 units every morning. The pruritus disappeared, but the pain became so acutely exacerbated that large amounts of Demerol and codeine had to be given, especially at night. Progressive weakness of the lower extremities accompanied the increased pain. Past history was not contributory except that he had had a severe depressive episode coincident with sharp financial reverses in the stock market crash of 1929. The present symptoms were accompanied by marked depression. There was no family history of diabetes.

Examination revealed a well developed and well nourished man. Blood pressure was 154/96 mm. of Hg. There were a few hemorrhages and exudates in the right fundus. The liver was palpable at the costal margin. All peripheral pulses were readily palpable. There was evidence of excoriation of the anterior aspects of both tibiae. Neurologic examination revealed weakness of both thighs, more marked on the left and involving the quadriceps more than the hamstrings; weakness of the left hip flexors; absence of both knee jerks (ankle jerks were present); and loss of vibratory perception in the left lower extremity.

Laboratory investigation revealed: Urine: specific gravity, 1.008; albumin, 2 plus; sugar, 1 plus; 12 red blood cells and one to two white blood cells per high power field. Hemoglobin, 14.4 gm.%; red blood count, 4.5 million per cubic millimeter; white blood count, 6,900 per cubic millimeter, with a normal differential. Blood Wassermann test, negative. Blood urea nitrogen, 14 mg.%; bilirubin, 0.2 mg.%; calcium, 10.1 mg.%; phosphorus, 3.4 mg.%; alkaline phosphatase, 6 King-Armstrong units; blood sugar, 140 mg.%. Lumbar puncture yielded clear, colorless fluid with no evidence of block. Colloidal gold, negative. Cell count, 0. Total protein was elevated to 63 mg.%.

Course: The diabetes was rapidly brought under control with the use of insulin and diet, but the symptoms and weakness increased. Simultaneously, the patient's depression became more marked and, although his diabetes was under excellent control, there was persistent weight loss as a result of the associated anorexia. This continued for three months. During this period of time, many other diagnoses were considered in view of the unresponsiveness of the condition and paucity of sensory findings. However, after the three months the patient began to improve, and the recovery proceeded at a remarkably rapid rate, so that two months later he was essentially back to normal. Follow-up report four and a half years later indicates that the patient has remained well, with no recurrence of these symptoms.

Comment: The typical onset of symptoms of uncontrolled glycosuria occurred fully eight months following the onset of the neurologic complaints, which clearly were the initiating clinical manifestations of the diabetes. Of added interest is the aggravation and worsening of the nerve involvement following the institution of good diabetic control. This has been noted previously.[8]

Case 3. This 65 year old widowed white female had developed severe backache four weeks prior to referral. The backache was migratory but was more pronounced in the cervical and upper thoracic spine area, was relieved by heat, and disappeared in about 10 days. Three days after the onset of backache she experienced numbness and coldness in the fingers and toes. This was soon followed by progressive stiffness and weakness of the hands and the lower extremities. She had no actual pain in the

lower extremities, but she described them as "feeling heavy and as though they do not belong to me." They became so weak, however, that she fell several times and was afraid to walk unaided. Accompanying these symptoms was a 10-pound weight loss associated with marked depression and anorexia. There were no sphincteric disturbances, headaches, visual difficulties or gastrointestinal manifestations, or any symptoms of uncontrolled glycosuria. Past history was negative except for a cholecystectomy 25 years before. Family history revealed that her mother and one sister had diabetes.

Physical examination revealed a well developed, well nourished female not appearing ill. Blood pressure was 140/80 mm. of Hg. The heart and lungs were normal. The liver and spleen were not palpable. The peripheral pulses were palpable. The cranial nerves were completely normal. The fundi did not reveal any hemorrhages or exudates. There was weakness of all muscle groups of the four limbs, with complete absence of all deep tendon reflexes; no pathologic reflexes were elicited; there was some atrophy of the thenar, hypothenar and interossei muscles. Sensory examination revealed impairment of vibration sense below the iliac crest, dystereognosis, impairment of two-point discrimination but intact position sense and touch; Romberg's test was positive.

Laboratory examination revealed hemoglobin, 13.6 gm.%; white blood count, 7,600 per cubic millimeter, with a normal differential. Urinalysis showed specific gravity, 1.026, without albumin or sugar. Fasting blood sugar, 86 mg.%; blood urea nitrogen, 12 mg.%; calcium, 9.5 mg.%; phosphorus, 3.4 mg.%; alkaline phosphatase, 8.7 King-Armstrong units; bilirubin, 0.39 mg.%; cholesterol, 231 mg.%; total protein, 7.3 gm.%; albumin, 4.2, globulin, 3.1; sedimentation rate, 28 mm. per hour; blood Wassermann test, negative. Electrocardiogram was normal. Gastric analysis showed free acid in all specimens. X-rays of the chest and skull were negative; x-rays of the spinal column revealed mild osteoarthritic changes in the thoracic and cervical spine, compatible with the patient's age.

The abnormal neurologic findings, consisting of symmetric weakness of all four extremities, absence of all the deep reflexes, presence of paresthesias and sensory changes, and the moderate atrophy of the small hand muscles, were highly suggestive of and consistent with diabetic neuropathy. This suspicion was furthered by the family history of diabetes. A glucose tolerance test was therefore done in spite of the presence of a normal fasting blood sugar of 86 mg.%. Results of this tolerance test were:

Time	Blood Sugar	Urine Sugar
Fasting	100 mg.%	0
½ hour	216 mg.%	0
1 hour	244 mg.%	3 plus
2 hours	296 mg.%	4 plus
3 hours	198 mg.%	1 plus

This abnormal result, of course, established the diagnosis of diabetes. A lumbar puncture with careful attention to the manometric readings was performed. The manometric studies, the Wassermann test, and the colloidal gold and cell counts were normal. However, the spinal fluid total protein was elevated to 75 mg.%.

In view of the absence of other neurologic diseases, the presence of proved diabetes, the typical neurologic findings and the elevation of spinal fluid protein, the diagnosis of diabetic neuropathy was established. The further course of this patient is of interest in that, shortly after her coming under observation, the symptoms began to clear spontaneously without therapy. Six weeks after the onset she began to notice return of strength and disappearance of paresthesias in all extremities. The improvement was progressive, so that in two and a half months after the onset her lower extremities were subjectively completely normal and the strength in the upper

extremities was almost entirely normal. It is interesting to note that, in spite of the marked improvement, the reflexes at this time are still absent and there is still some atrophy of the small hand muscles. With the return of power in all extremities there was a concomitant return of vibratory and other impaired sensations. In addition, the marked depression which had manifested itself with the onset of symptoms also disappeared.

Comment: This case indicates that diabetic neuropathy may well be the initial manifestation of diabetes mellitus. In this patient it is so far the only manifestation. The clues leading to the establishment of this diagnosis were (1) the nature of the neurologic signs and symptoms, and (2) the family history of diabetes. This was confirmed by the absence of any other neurologic disease, the elevation of the spinal fluid protein and the positive glucose tolerance test. Even though the patient has now been followed for six months, there have been as yet no signs or symptoms clinically indicative of disordered carbohydrate metabolism.

Case 4. This 65 year old white male had first come under observation 16 years before. His history from 1941 until the present episode consisted essentially of frequent routine check-ups because of a heart murmur discovered in 1918, associated with occasional bouts of extrasystoles and paroxysmal tachycardia. In 1948 he developed an episode of painless hematuria, which proved to be due to a congested prostatic urethra. During this period of observation, his blood pressure slowly increased to 190/110 mm. of Hg. In 1951 he sustained an acute myocardial infarction. In 1953 he had an episode of acute paroxysmal tachycardia associated with coronary insufficiency. In 1954 he had another minor coronary thrombosis. In 1956 he again experienced acute coronary insufficiency associated with paroxysmal arrhythmia. During all this time, and particularly during the episodes of serious illness, some of which required hospitalization, there were repeated urinalyses, none of which revealed the presence of sugar. In addition, there were many fasting blood sugars, all normal.

The present illness had its onset in May, 1957, with the complaint of pain in the low back region, which the patient thought might have followed a sprain. This pain improved, but 10 days later was followed by pain in the right lower extremity associated with stiffness and a pulling sensation in the knee and thigh. This pain was worse at night, and seriously interfered with his sleep. There were no symptoms indicative of uncontrolled glycosuria; there were no sphincter disturbances.

Examination revealed a well developed, well nourished white male, not appearing ill, complaining of pain in his right lower extremity and difficulty in walking. Blood pressure was 180/98 mm. of Hg. The heart was enlarged to the left, with a grade II systolic murmur at the apex transmitted into the left axilla. The lungs were clear; abdomen, negative; rectal examination, negative. The cranial nerves were intact. Examination of the fundi showed moderate sclerosis of the retinal vessels without hemorrhage or exudates. Examination of the extremities showed diminution of the right knee jerk as compared with the left; a right Babinski's sign was present; vibration sense was absent below the iliac crests; there was slight but distinct weakness of dorsiflexion of the right foot, knee and hip.

Laboratory examination revealed hemoglobin, 14.8 gm.%; white blood count, 8,400 per cubic millimeter, with a normal differential. Urinalysis showed specific gravity, 1.028; albumin, 1 plus; sugar, negative; occasional hyaline cast. Sedimentation rate, 21 mm. per hour; fasting blood sugar, 121 mg.%; calcium, 11.4 mg.%; phosphorus, 1.9 mg.%; alkaline phosphatase, 7.8 King-Armstrong units; acid phos-

phatase, 2.2 units; cholesterol, 256 mg.%, with ester, 213 mg.%; total protein, 6.9 gm.%; albumin, 4.4, globulin, 2.5. Blood Wassermann test was negative. X-ray of the chest showed the heart to be enlarged to the left with the aorta elongated and tortuous. X-ray of the lumbar spine showed mild hypertrophic changes. X-ray of the right femur and hip showed no abnormalities. Lumbar puncture revealed clear, colorless fluid under normal pressure, with completely normal manometric readings, cell count, Wassermann and colloidal gold. However, the total spinal fluid protein was elevated to 84 mg.%. Electroencephalogram was normal.

In view of the onset, the nature of the findings, the elevation of the spinal fluid protein and the presence of a fasting blood sugar of 121 mg.%, it was suspected that this was a manifestation of diabetic neuropathy. Although the family history was said to be negative for diabetes, more persistent questioning of other members of the family revealed that the patient's paternal uncle and the daughter of this uncle both had diabetes. A glucose tolerance test was done, which revealed the following:

Time	Blood Sugar	Urine Sugar
Fasting	129 mg.%	0
½ hour	246 mg.%	0
1 hour	316 mg.%	4 plus
2 hour	281 mg.%	4 plus
3 hour	183 mg.%	4 plus

It was now evident that the patient had both diabetes and diabetic neuropathy. The latter presented with the syndrome of "femoral nerve" paralysis, as has been previously described in diabetes.[6, 16] The distribution of the findings as well as the presence of Babinski's sign clearly pointed to involvement of the spinal cord.

The further course of this patient is of interest in that, within three weeks after onset, improvement in power began. This improvement progressed so that within two months function was almost completely normal. However, although Babinski's sign had disappeared, the right knee jerk was still slightly hypoactive as compared with the left, and the tonus in the right quadriceps muscle was decreased as compared with the left.

Comment: This patient had been observed at frequent intervals over a long period of time during which he had never manifested any of the clinical signs, symptoms or laboratory findings of diabetes mellitus. His initial onset of clinical diabetes was manifested by an asymmetric type of myeloradiculoneuropathy, accompanied by a borderline elevation of fasting blood sugar, with diabetes mellitus confirmed by a glucose tolerance test. The latter test was performed because of the clinical suspicion that this could be diabetic neuropathy, the suspicion being further strengthened by the family history. This patient is under close observation and now, four months later, still exhibits no clinical signs or symptoms associated with hyperglycemia and glycosuria.

Case 5. This was the first admission of a 74 year old white male complaining of numbness in his feet and lower chest. The patient had been well until four years before, when he noted numbness of both feet, accompanied by tingling in the toes. These symptoms became progressively worse. Three years before he had begun to have chronic aches in the knees, spreading up towards the hip, and a sensation of coldness along with the numbness and tingling in the feet. The pains were characteristically worse late at night and in the early morning. He developed progressive weakness of the lower extremity, so much so that he had fallen on occasion. Two

years before (two years after the initial onset of his neuropathy) he developed diabetes, with the classic onset of polyuria, polydipsia and weight loss. He was now treated with insulin and diet, following which there was relief of symptoms except for persistence of soreness and numbness of the feet. Seven months before he had developed numbness and a feeling of heaviness around the waistline. While in the outpatient department he had received vitamin B_{12} injections, 1,000 μg. daily for several weeks, with no beneficial effect.

On examination the patient was well developed and well nourished, and did not appear to be acutely ill. The heart and lungs were normal. Blood pressure was 150/74 mm. of Hg. A smooth liver edge was felt two fingerbreadths below the costal margin. The dorsalis pedis pulse was not felt in the left foot; all other pulses were present. Neurologic examination revealed miotic pupils, not reacting to light; three small hemorrhages characteristic of diabetic retinopathy were seen in the right fundus. There were absence of knee jerks and ankle jerks bilaterally, and diminution of the deep tendon reflexes in the upper extremities. There was considerable atrophy of all muscle groups, most marked in the quadriceps, with weakness in extension of the knees; muscle tenderness of both thighs was present. Sensory examination revealed decreased pinprick and temperature sensation over the feet and legs, without a definite level; vibratory sense was impaired from the iliac crest peripherally.

Laboratory examination: urinalysis, negative; hemoglobin, 12 gm.%; white blood count, 7,800 per cubic millimeter, with a normal differential. Erythrocyte sedimentation rate, 8 mm. per hour; blood urea nitrogen, 14 mg.%; total protein, 6.7 gm.%; albumin, 4; globulin, 2.7; blood serology, negative. A two-hour postprandial blood sugar was 235 mg.%. X-rays of the chest and the dorsal lumbosacral spine were all negative except for some mild osteoporosis and mild hypertrophic changes. Lumbar puncture was completely negative except for elevation of the total protein to 121 mg.%. Gastric analysis revealed the presence of free acid.

Comment: This patient had all the characteristic signs and symptoms of diabetes and diabetic neuropathy, including elevation of the spinal fluid protein. The classic picture of diabetic neuropathy had been present fully two years before he developed the symptoms of diabetes. It is of interest that, at his advanced age, the onset of the symptoms of uncontrolled glycosuria was precipitous.

Case 6. This was the first Mt. Sinai Hospital admission of a 60 year old white male with the chief complaint of pain in both lower extremities for the last eight months. Past history was significant in that one year before he had had a cerebral vascular accident, with temporary right-sided paresis and aphasia. Eight months before, apparently unrelated to the preceding stroke, he had noted pain in both thighs, calves and feet, increasing in severity. The pain was almost always nocturnal, being described as a cramp, worse in the supine position, severe enough to prevent sleep and relieved by walking. He was referred for the possibility of a spinal cord neoplasm. During this time he had marked anorexia, accompanied by a 35-pound weight loss without polyuria or polydipsia. There was no previous history of headaches, visual disturbances, intermittent claudication or diabetes. Family history was negative for diabetes.

On examination the patient was well developed and not acutely ill. Fundi were negative, without hemorrhages or exudates; the pupils were normal. The heart was normal in size; auricular fibrillation was present; blood pressure, 170/80 mm. of Hg. The lungs were clear. The liver was palpable two fingerbreadths below the costal margin. The peripheral pulses were palpable and normal; there was no peripheral

edema. Neurologic examination revealed a residual old right hemiparesis with a mild expressive aphasia; there was mild generalized weakness of both lower extremities; all deep tendon reflexes were absent except those of the right upper extremity. Oscillometric readings of the lower extremities were normal.

Laboratory findings: Urine: specific gravity, 1.020; 2 plus albumin; an occasional white blood cell without casts, and no sugar. Hemoglobin, 14 gm.%; white blood count, 9,000 per cubic millimeter, with a normal differential. Erythrocyte sedimentation rate, 37 mm. per hour; blood urea nitrogen, 7 mg.%; total protein, 7.5 mg.%, albumin, 4.1, globulin, 3.4; cholesterol, 234 mg.%; alkaline phosphatase, 5.1 King-Armstrong units; acid phosphatase, 1.1 units.

Although the history and evidences of clinical diabetes were completely lacking, the signs and symptoms referable to this patient's neuropathy were so strongly suggestive that a clinical diagnosis of diabetes was postulated on the basis of this observation and previous experience. This was confirmed by fasting blood sugar levels of 133 mg.% and 159 mg.%, and a two-hour postprandial level of 222 mg.%. As further confirmation, a lumbar puncture was performed which was completely negative in all details except for the elevation of the total spinal fluid protein to 62 mg.%. On bed-rest and a diabetic diet the symptoms gradually tended to disappear, and the appetite returned. Follow-up information disclosed that the improvement has continued.

Comment: This case indicates that familiarity with the usual manifestations of diabetic neuropathy, plus an awareness of the fact that these findings may present themselves prior to any other manifestations of diabetes mellitus, will lead to the correct diagnosis, indicated therapy and a diminution in the severity and duration of symptoms.

Case 7. This was the first admission of a 21 year old Puerto Rican male complaining of severe pains in his legs and back for the last year. The pain was accompanied by marked lethargy and fatigability, so much so that, although he was an accomplished athlete, he was forced to stop all such activity. The pain was dull in character and located chiefly in the ankles and knees, was aggravated by rest and always worse at night, tending to disappear during the day. Two months after the onset of the pains he developed anorexia, accompanied by polyuria, polyphagia and a 25-pound weight loss. He was admitted to the Mt. Sinai Hospital in moderate ketosis.

Physical examination revealed a severely malnourished, thin male. Blood pressure, 110/70 mm. of Hg; pulse, 104; respiration, 20. The remainder of the examination was negative except for calf tenderness and the absence of deep tendon reflexes in the lower extremities.

Laboratory examination: Urine: specific gravity, 1.026; 4 plus glycosuria and acetonuria. Hemoglobin, 15.6 gm.%; white blood count, 12,700 per cubic millimeter, with a normal differential. Fasting blood sugar, 220 mg.%; blood urea nitrogen, 11 mg.%; blood sodium, 131 mg.%. Blood Wassermann test, negative. Lumbar puncture was entirely normal except for elevation of the spinal fluid protein to 57 mg.%. X-ray examination of the chest was normal.

Course: The patient was quickly brought out of ketosis and his diabetes was well controlled on a 2,500 calorie diet with 50 units of lente insulin daily. Following establishment of diabetic control, he was discharged to the diabetic out-patient department. Within the next month, during which time he was maintained on excellent diabetic control, there was slow but progressive improvement in his legs and progressive diminution in pain.

Comment: The neuropathy in this instance was so incapacitating that the patient had to give up any physical endeavors prior to the occurrence of the classic symptoms of uncontrolled diabetes mellitus. It is noteworthy that his neuropathic symptoms improved with the establishment of good diabetic control.

Discussion

The foregoing observations indicate that neuropathy may be the presenting symptom of diabetes mellitus and thus antedate the appearance of other manifestations of this disease. The implications are both practical and theoretic.

From the practical, clinical point of view, it is apparent that an awareness of this will result in establishing the correct diagnosis, lead to the earlier recognition of diabetes mellitus, the application of known preventive measures wherever feasible, the institution of a proper therapeutic regimen, and the further reduction of cases now relegated to the "idiopathic" category. Root and Rogers [17] state: "Diabetes should be suspected in cases of obscure pain and paralysis of the legs just as it is in the presence of gangrene, furunculosis or the classic symptoms of the disease." Certainly the place of "latent" diabetes in the differential diagnosis of nervous lesions deserves greater emphasis than it has received in the past.

Any neurologic picture compatible with or suggestive of the syndromes associated with diabetic neuropathy and/or occurring in a patient with a family history of diabetes must be investigated for the possibility of diabetes mellitus. Unfortunately, the usual diagnostic procedure is the determination of the fasting blood sugar. This is perhaps the least rewarding test in such situations. A normal value only too frequently results in discarding the diagnosis without further consideration. It is much more logical and productive to determine the two-hour postprandial blood sugar level as a screening test, and then to perform a glucose tolerance test as indicated. Such an approach may help to solve some hitherto obscure and unrecognized instances of diabetic neuropathy, as illustrated by cases 1, 3, 4 and 6.

From the theoretic point of view the implications are most intriguing. During the last several years there has been a growing awareness that diabetes mellitus is a generalized, complex, fundamental disease process with many facets. The carbohydrate metabolic disorder is only one of these facets, although its train of symptoms is the most commonly recognized. Other suggested facets include the complications of pregnancy, microangiopathy comprising retinopathy and nephropathy, and arteriosclerotic involvement of the larger vessels.

The complications of pregnancy associated with diabetes may occur many years before the eventual development of diabetes, and are identical with those occurring in the diabetic state. These well documented phenomena

include the production of overweight, edematous babies, a marked increase in stillbirths and neonatal fatalities, an increase in the number of congenital abnormalities, and hypertrophy of the islets of Langerhans in the offspring. Recognition of these features has led to the performance of glucose tolerance tests which have established the existence of a so-called "prediabetic" state long before the clinical onset of diabetes.[18, 19]

In considering the vascular complications, Dolger [20] pointed out that vascular damage should no longer be considered as a complication but be recognized as a basic manifestation of the disease. Cases of retinopathy have been recorded where the only evidence of diabetes mellitus was a positive glucose tolerance test.[21] Recently, two cases of renal failure associated with Kimmelstiel-Wilson lesions of the kidneys and neuropathy have been reported; [22] these were the only clinical manifestations of diabetes mellitus. Ditzel [23] has reported alterations of the conjunctival blood vessels before clinical diabetes is manifest. Dry and Hines,[24] in describing the arteriosclerotic involvements in diabetes, conclude that this is "merely another facet of the same crystal," and that it would be more nearly correct to regard the problem in the light of an abiotrophy affecting both the insulin-producing tissues and the vascular system.

The observations reported in this paper—namely, that diabetic neuropathy may be the initial clinical manifestation of diabetes, that it is not dependent upon the presence of prolonged hyperglycemia and glycosuria, and that it need not necessarily depend upon the control of hyperglycemia for therapy—would indicate that the neuropathy is not a complication but rather is an integral part of the syndrome of diabetes mellitus. Hence it would take its place as "another facet of the crystal."

In brief, our findings would serve to strengthen the doctrine that diabetes mellitus is not limited to a disorder of carbohydrate metabolism but has many separate features which are, in some as yet undefined way, related to each other much as are the spokes of a wheel. These would include at the present time (1) the derangement of carbohydrate metabolism, (2) the complications of pregnancy, (3) microangiopathy, (4) arteriosclerosis, and (5) neuropathy.

Summary

1. Representative cases are reported to indicate that diabetic neuropathy may be the initial clinical manifestation of diabetes.

2. Awareness of this occurrence and its diagnostic application should help resolve some hitherto obscure clinical problems.

3. Diabetic neuropathy should be regarded as a concomitant and integral feature of diabetes mellitus, rather than as a complication of the disease.

SUMMARIO IN INTERLINGUA

Usque nunc il esseva generalmente acceptate como un facto que le complicationes neurologic de diabete mellite seque post un prolongate periodo de inadequate regulation diabetic. Le hic presentate documentation de casos indica que isto non es necessarimente assi. De facto, in le casos del presente reporto, neuropathia diabetic se monstrava como le prime manifestation clinic de diabete mellite, non accompaniate de symptomas de hyperglycemia o glycosuria. Le diagnose de diabete mellite esseva suspicite super le base del tableau clinic, del constatationes in le fluido spinal, e del historia familial. Le diagnose esseva confirmate per le pertinente investigationes laboratorial.

Iste observation ha consequentias tanto ab le puncto de vista clinic como etiam ab le puncto de vista theoric. Ab le puncto de vista clinic, il es a expectar que si on presta attention a iste possibilitate e prende lo in consideration in le diagnose, on va poter resolver plure problemas clinic que usque nunc debeva remaner obscur. Omne syndrome neurologic que es compatibile con neuropathia diabetic o mesmo suggere lo, specialmente si le patiente in question ha un historia familial de diabete, debe esser investigate con respecto al possibilitate de diabete mellite.

Ab le puncto de vista theoric, le hic reportate observation suggere que neuropathia diabetic debe esser reguardate como un aspecto concomitante e integral de diabete mellite, plus tosto que como un complication de illo. Isto reinfortia le doctrina que diabete mellite non es restringitemente un disordine del metabolismo de hydrato de carbon sed plus tosto un processo pathologic fundamental que possede multe aspectos. Istos include le disordine del metabolismo de hydrato de carbon, le complicationes del pregnantia, microangiopathia, arteriosclerose, e neuropathia.

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THE MANAGEMENT OF THE SUICIDAL PATIENT*

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It is always sound medical practice to "treat the disease rather than the symptom," and this dictum is especially important when caring for patients who suffer from maladies where suicidal potentialities are present. Karl Menninger, in his book, *Man Against Himself* points out the fallacies that lie behind the popular notion that "suicide is an escape from an intolerable life situation." [1] He stresses that suicide is the result of a deep-seated personality derangement and not merely a reaction to some immediate stimulus in the environment. This same reasoning detracts from the importance of external catastrophes—national or international conflicts, financial depressions or reverses—as major factors in the rate of deaths by suicide. If the suicidal patient is going to be handled properly and effectively, the symptom must be viewed in its proper perspective—the presenting sign of an underlying illness. As no physician would dismiss a patient with hemoptysis without a complete investigation, likewise the treatment and care of the suicidal patient do not rest in resuscitative or reparative measures alone. The underlying malady that threatens man's strong instinct to preserve life must be carefully evaluated and treated. It is then, and then only, that the symptom can be effectively controlled.

Incidence of Death by Suicide

Sixteen thousand suicides are reported in the United States each year, as well as approximately some 100,000 suicidal attempts. As statisticians will confirm, these figures are on the low side because of the difficulties that surround attempts at converting such untimely deaths into figures. Seventy per cent of the persons who committed suicide in 1945 were not hospitalized at the time. Of the remainder, 23% more suicides occurred in general hospitals than in mental hospitals.[2] These figures accentuate the fact that this problem may fall into the hands of any physician, regardless of specialty and type of practice.

Classification of Suicidal Patients

Suicide is a symptom common to a number of different types of personality disturbance, and the following classification is presented as a guide to the type of conflict that can lead to self-destruction.

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I. *The Acutely Depressed Patient.*

A. *Involutional melancholia.* Man faces his greatest suicidal threat between the ages of 45 and 64. This period corresponds to those two decades in the life span during which depressions of a severe type are most likely to occur. The mechanism that gives impetus to the forces of self-destruction is the same as that which underlies the depression itself. Generally, depressed suicidal patients have throughout life harbored various destructive tendencies but have been able to control them effectively. Prior to the involutional period, those energies that would otherwise have been self-destructive were directed outward and were manifested in a life of rigid control and discipline. Such overdevotion to duty and extreme self-control may have appeared to the casual observer to have been the epitome of altruism. In the involutional period the patient, faced with the feeling that life's task has been accomplished, sees no channel into which he can continue to direct his energies. They are then directed against the self, and the result is severe depression with strong suicidal potentialities.

B. *Manic depressive psychosis, depressed type.* In the depressive phase of this illness, suicidal ruminations are frequent and the impulse is often acted upon. When the patient is severely depressed psychomotor retardation is a common symptom, and this retardation may be so severe that the patient literally has not the energy to carry out his destructive impulses. In the convalescent phase, when the retardation is less severe, the patient presents a greater suicidal threat.

The causes of this form of depression are not definitely known. There is evidence to suggest that heredity may exercise a predisposing influence, but the mechanism through which it may act is not known. Individual constitutional factors may predispose to this affective diathesis, but the psychotic manifestations and symptoms are colored by the individual's sociopsychologic experiences in life.

II. *The Schizophrenic Group.*

Among schizophrenic patients, suicide is more common in the paranoid group than in any of the other subgroups. The attempts at self-destruction effected by such patients are often brutal and horrifying. Their attempts may be prompted by hallucinations or bizarre delusional ideas. A paranoid schizophrenic may experience an auditory hallucination commanding self-destruction and obey it implicitly without warning. The delusional patient may labor under the belief that by continuing his life he may bring endless destruction and disaster to other people or to the universe. To such a patient, self-destruction is a worthy sacrifice of one life in lieu of many.

III. *The Neurotic Group.*

It was originally thought that neurotic patients were not subject to bona fide suicidal impulses, and that their successful attempts were the result of

miscalculations. It is true, in some instances, that there is a large attention-gaining element in operation, and the attempt is therefore directed toward controlling the environment. Such suicidal attempts are carried out under circumstances not likely to succeed. An example of such is the woman who turns on the gas when she hears her husband turning in the driveway. In other cases the attempt is the result of a serious and deep-seated, destructive desire directed against the self. Zilboorg postulates that the well known childish fantasy, "When I am dead they will be sorry," finds its literal expression in self-murder.[8] Attempts resulting from such a disturbance are designed toward a successful end.

IV. *Self-Mutilations.*

Self-mutilation consists of deliberate destructive attacks upon various parts of the body, e.g., the plucking out of an eyeball, or the cutting off of a limb or the genitalia. These acts are a compromise form of suicide in which a part is sacrificed in lieu of the total organism. The unconscious factors found here are similar to those underlying most suicides. These acts frequently have a religious expiatory flavor, and are often the literal interpretation of the well known Biblical quotation, "And if thy right eye offend thee, pluck it out, and cast it from thee; for it is profitable for thee that one of thy members should perish, and not that thy whole body should be cast into hell. And if thy right hand offend thee, cut it off, and cast it from thee; for it is profitable for thee that one of thy members should perish, and not that thy whole body should be cast into hell." (St. Matthew, Chapter V, Verses 29, 30.)

V. *The Accident-Prone Group.*

Factors which motivate accident-prone behavior are similar to those which motivate more direct methods of self-destruction. In contrast to the other suicidal patients, those who fall into the accident-prone group are not consciously aware of their objective, which is the destruction of the self. They attribute their ill luck to fate, and strongly deny any personal liability. They are not aware of their immediate goal, and therefore their death is sought by accidental means rather than by a deliberate, self-arranged suicidal attempt.

VI. *Physiologic Suicide.*

Every physician is familiar with the case of the diabetic patient who will not adhere to his dietary régime, and the cardiac patient who will not live within his reserve. Such patients are committing suicide as surely as those who take their lives by more dramatic means. However, they are not consciously aware of their self-destructive goal. The motives leading to such behavior are outside of the patient's range of awareness—they are, in fact,

subconscious. It may require that the patient be in psychotherapy for an appreciable time before he can fully accept and appreciate what such behavior means. When the patient has gained such awareness, it is then the task of treatment to try to uncover the personality difficulties that are prompting this destructive solution.

VII. *The Acute Anxiety Attack.*

When an attack of anxiety is so severe that it reaches panic proportions, suicide becomes a definite possibility. The patient in panic is so disturbed and uncomfortable that he will impulsively kill himself to get rid of his feelings of extreme horror or fright. Such patients should be heavily sedated and transferred without delay to a protective hospital environment. Actual physical restraint may be necessary as an emergency measure of protection.

Indicators of Potential Suicide

Pay heed to the warnings of the patient. They may be subtle and vague, or frank and unmistakable. Some of the ways to recognize or suspect suicidal intent are set forth below.

Contrary to the belief that suicidal patients carry out their act under a well-guarded screen of secrecy, many of them talk about their intent beforehand—possibly as many as 40%.[4] If the patient does not volunteer information, leading questions may help to elicit underlying suicidal tendencies. Such questions should be clothed in simple, direct yet friendly words. The response obtained cannot always be taken at face value. The most reassuring reply is a qualified denial, like, "Yes, I wish I were dead but I would not lay hands on myself." A simple "No" in a depressed patient carries little assurance. An outburst of anger or indignation is to be viewed with suspicion, and an increase in agitation or a flood of self-accusations is pointedly significant.

Forewarnings of self-destruction are often conveyed in less obvious and more subtle ways. Careful attention should be paid to the patient's selection of reading material. Sometimes topics dealing with death, despair and doom may herald a catastrophe. Daily newspapers are filled with accounts of such perusals prior to the death leap. Such readings are recognizable as an offspring of the more renowned "suicidal note." Carelessness in personal appearance, in dress and in bodily hygiene, especially when of recent origin, may also express the feelings of underlying wretchedness that lead to suicide.

A history of a previous suicidal attempt is important, since depressed patients often make repeated attempts. Physical signs, such as transverse scars on the wrists or neck, point to previous attempts at suicide.

Such heraldic signs should never be ignored, and are to be viewed with more suspicion during the seasons of highest suicidal incidence. It is a well known fact, but one which lacks satisfactory explanation, that suicidal rates show a sharp rise in the spring and fall.

A wealth of valuable information can be gained from the surrounding circumstances and the nature of the attempt. The more impulsive the suicidal attempt, the sooner and more apt is remorse likely to appear. Remorse is of value in diminishing the intensity of the desire to try again. The more deliberate the act, the less remorse or regret will be present and the greater the lag period before it appears.[5] The degree of ritual attached to the preparation of the boudoir of destruction is in direct proportion to the patient's intent. The patient who dresses up and arranges the scene in an orderly fashion is striving for a successful attempt. In an effort to explain the significance of such ritual, Zilboorg[8] postulates "that what is ritualistically compulsory in the primitive community does not disappear from the psychic life of the civilized person. It merely recedes into the background of the unconscious and under proper circumstances of psychological stress makes its appearance in the form of irrational impulsiveness, so frequently observed among suicidal persons of the white race."

There are no absolute criteria to follow in this evaluation. The decision whether a particular patient presents a serious suicidal risk is ultimately a matter of judgment based upon the information available to the physician at the time of his examination.

Management of the Suicidal Attempt

When a physician is called upon to care for a patient who has made a suicidal attempt, the appropriate emergency measures, such as gastric lavage, the use of emetics, the control of hemorrhage, artificial respiration, etc., will have to be applied.

The scene of the attempt often holds evidences that are invaluable in determining the nature of the agent used by the patient. It is advisable to scan the immediate surroundings for empty containers that might provide a clue so that effective corrective measures can be taken and antidotes prescribed. Immediate family members and relatives may be able to advise if the patient has been in the habit of taking drugs, and even though no container be found, they can often supply the name of the pharmacy where the patient has prescriptions filled. If the patient has been under the care of a doctor recently, he may be able to give pertinent data covering the patient's habits and difficulties, and the drugs he has been accustomed to taking. When the physician arrives the patient may be comatose, and immediate hospitalization will be indicated. A call to the emergency room of the local hospital, giving all available information, will save precious minutes in addition to advising them such a patient is arriving. It will also enable the hospital to secure the services of an anesthesiologist at once. Such life-saving measures as establishing artificial respiration and positive pressure breathing are part of his daily work. He is also familiar with the most desirable types of antidotes and those supportive measures, such as fluid and electrolyte balance, which are of such vital need to the comatose patient.

His skill in the daily use of barbiturates and anesthetics especially qualifies him to help.

Certain explanations and advice are owing to the distraught family and relatives of the patient. The attempt should be explained to them as an indication that the patient is suffering from a serious emotional illness and that it is an illness that will have to be properly evaluated and treated. If the attempt is a relatively minor one, the family may offer various suggestions about treatment, such as a period of vacation or rest at home in view of the fact that the patient has been overworked. It is dangerous and inadvisable to subscribe to such measures, as there is no guarantee that the patient will not make another and perhaps more successful attempt.

When the immediate needs have been attended to, it is important to place the patient in an environment where further attempts can be prevented. This often calls for constant observation, since it is only by such constant vigilance that the patient can be afforded the protection needed. It is well to remember that in the period of relative calm following the stormy initial sequence of events, the patient can again become actively suicidal. This is especially true of the depressed patient. In the early stages of recovery from a depressive episode the patient often is more actively suicidal than during the depth of the depression.

When the immediate battle for life has been won, it is then necessary to evaluate the factors which contributed to the suicide in order that therapeutic efforts can be made to restore an emotional equilibrium. A psychiatric opinion and a complete evaluation of the illness that led to the suicidal attempt should be requested. When such evaluation has been obtained, appropriate plans for the long-term treatment of the patient can be formulated.

The psychiatrist will make every attempt to elicit all of the patient's symptoms. By doing so he gains the confidence of the patient, since the latter realizes that the doctor is now familiar with the thoughts, feelings and impulses that plague and horrify him. The sharing of these feelings, especially feelings heavily tinged with guilt, is good for the patient, since it helps to diminish their intensity. An attitude of optimism, support and reassurance on the part of the doctor is often more effectively conveyed in approach and manner than in words. However, verbal reassurance can and should be used to support this attitude. Verbal support has to be repeated frequently, because the sense of misery and despair is of such intensity that an isolated statement can be quickly forgotten. It is advisable to see the patient daily at this time. Freedom for contact by telephone or otherwise outside of the scheduled visits is advisable and often necessary.

The use of somatic therapies, such as electric shock or insulin coma, may be necessary to help the patient over the immediate critical phase of the illness. Electroshock therapy has an almost specific effect in lifting depression. Some of the newer chemotherapeutic agents can be of help, but a word of caution seems indicated, especially regarding the use of reserpine

and chlorpromazine in the depressed patient, since these drugs have been known to intensify the depressive diathesis. Benzedrine, Dexedrine and the new amphetamine-like substances may be of use in mild depressions.

The treatment of the suicidal patient extends beyond the immediate care of the impulse. Therapy should aim at effecting a resolution of the underlying causes; otherwise, there is every likelihood that the symptoms will return. The somatic treatments and chemotherapy in themselves do not bring about such a resolution. They help in restoring the patient to a temporary period of emotional equilibrium, during which time the process of psychotherapy is begun. The patient remains a suicidal risk until corrective emotional and personality changes have been effected.

There are occasions when such a course of prolonged therapy is not possible. In such cases, responsible members of the family should be instructed to watch for signs of impending relapse. Anorexia, weight loss, disturbed sleep, carelessness in appearance and lack of interest are early signs of the depressive syndrome. Drinking is an especially difficult problem. The depressed patient will often drink to relieve his suffering, but in so doing a vicious circle is set in motion. Alcohol initially soothes, but when its calming effects wear off it leaves in its wake more intense feelings of guilt and depression. A serious depression may at times masquerade under the guise of physical illness. Somatic delusions are frequent in their occurrence in the involutional-type of depressions. If there are no physical findings to substantiate somatic illness, it is well to remember that the symptom may be representative of the well recognized delusional triad covering health, wealth and worth. The fear of a malignant disease such as cancer is quite common, and a pronounced weight loss may add further to this suspicion. The weight loss may be the result of anorexia due to depression, or of a frank refusal of food in an attempt to bring about the desired end. In cases such as the latter, artificial feeding by gavage, subcutaneous clysis and intravenous fluids are life-saving emergency measures.

Among the group of schizophrenic patients who are suicidal, any recurrence of psychotic behavior, such as the expression of delusional ideas or the response to hallucinatory phenomena, merits careful watch and the consideration of further hospitalization.

It may not be possible to have every suicidal patient placed in a hospital because of existing environmental factors. When such patients must be treated at home, a room on the ground floor is safer for sleeping than one several stories up. Arrangements should be made for a responsible adult to stay in the same room. During waking hours someone should keep careful watch. Most suicidal attempts in depressed patients are carried out around four or five o'clock in the morning, because of the associated characteristic sleep disturbance. The depressed patient does not usually have much difficulty in going to sleep, but rather wakes in the early morning and is unable to go back to sleep. For this reason, long-acting sedatives in adequate

dosage should be prescribed. In moderately severe depressions the sex drives are diminished, and it is wise to discourage sexual activity, since impairment of this function can increase the patient's feelings of failure and worthlessness.

With the advent of the neuropsychiatric unit in many general hospitals, the doctor is faced with the problem of deciding whether the patient should be treated in a general hospital or in a psychiatric hospital. This decision will rest upon the type of illness that has evoked the suicidal attempt. The neuropsychiatric unit in the general hospital can be used to its greatest advantage in caring for an illness that is likely to respond to short-term treatment. Depressions, especially involutional melancholia and, to a lesser extent, manic depressive patients, can usually be expected to respond to electroshock treatments. After this has been accomplished, further appropriate psychotherapy can be carried out on an out-patient basis. Cases of neurotic suicidal drives with definite precipitating environmental factors can often be treated in a general hospital. Among the schizophrenic group of illnesses, fewer patients will be found suitable for care in the general hospital, since a longer course of treatment is indicated and long-term psychotherapy may be necessary. Similar factors govern the care of the self-mutilating group, and those depressed patients who fail to respond to adequate somatic therapy or who suffer an early relapse. There are occasions when a potentially suicidal patient cannot be hospitalized without imposing hardship on the family. If the patient is the breadwinner, pressure may be put upon the physician to allow the patient to stay at home and continue working. In any depression that has assumed moderately severe proportions, the patient should not be allowed to continue working, because the associated impairment in his intellectual function will cause a definite falling off in his skills and an increase in feelings of worthlessness.

The suicidal patient who is determined in his striving toward self-destruction is relentless and adept in his quest for an instrument of death. An apparently innocuous article of household furniture or article of personal apparel may in the face of necessity be turned into a weapon of destruction. In spite of maximal precautions, patients have been known to commit suicide. Since there are no absolute criteria that can be successfully used in evaluating suicidal potentialities, it is impossible to prevent all suicidal attempts or deaths. However, whether the patient is to be treated at home or in a hospital, constant vigilance is the most effective preventive measure. Therein lies the hope of reducing the current high rate of suicidal deaths.

Summary

The suicidal attempt is a symptom, and not a disease in itself. It is the presenting sign of a serious underlying emotional difficulty. Treatment should therefore be directed toward the entire emotional disorder and not the isolated symptom. The immediate goal in treatment is to prevent the

patient from following his path into the abyss of destruction. To achieve this, various methods of emergency control need to be instituted and, at times, life-saving resuscitative and reparative measures used. When the immediate battle for life has been won, the underlying disease that gave rise to the symptom must be treated. It is a symptom common to a wide variety of diseases that fall into the category of emotional illnesses. It is by treating the underlying emotional disturbance that the patient can best be spared from such useless destruction of life.

Just as the causative illnesses are varied, so also are the methods of treatment. Individual cases call for different therapeutic approaches, varying from psychotherapy to chemotherapy and the somatic forms of treatment. In most cases hospitalization is necessary. Short-term treatment problems can be handled in the neuropsychiatric units of general hospitals, whereas longer term treatments are best carried out in psychiatric hospitals.

Prevention is the key to success, and it is by exercising such prophylactic measures that the current high rate of deaths by suicide can be reduced.

Summario in Interlingua

"Tractar le morbo plus tosto que le symptoma" es un principio medical specialmente applicabile al problema del suicidio. Le tendentia al suicidio es un signo de serie subjacente difficultates emotional. In istos il pote tractar se de un depression (de character endogene o reactive), de un reaction schizophrenic (specialmente del varietate paranoiac), de un stato acute de panico, o de un reaction neurotic. Le patiente predisponite "per fato" a suffrir accidentes e le patiente qui se destrue per medios physiologic (p.ex. le cardiaco qui refusa viver intra le limites de su reservas physic) representa gruppos special in que le suicidio non es cercate como un objectivo conscie sed plus tosto como un objectivo inconscie. Tal patientes committe suicidio tanto assecuratemente como le patientes qui destrue lor vita per medios plus dramatic. Actos de auto-mutilation es un forma de compromisso con le suicidio in que un parte es sacrificate in loco del toto.

Prevention es le clave al successo in le tractamento del patientes con potentialitates suicidal. Per consequente, attention debe esser prestate a omne signos que annuncia possibilemente un tal intention. Un grande numero del patientes (estimate a 40%) da pre-aviso de lor acto. Iste pre-aviso pote esser completemente patente e facilemente demonstrabile per directe questiones adressate al patiente, o illo pote esser subtilissime, exprimente se p.ex. in negligentia del vester o del hygiene personal, in le selection del lectura, o in le recurrentia de symptomas (hallucinationes, depression, alcoholismo, etc.) que precedeva un previe tentativa de committer suicidio. Patientes deprimite require le plus caute observation durante le prime phases de lor convalescentia, proque il es possibile que illes es alora plus suicidal que al culmine de lor stato depressive. Il existe nulle criterios absolute pro le evalutation del potential suicidal. Le judicamento del medico pote basar se solmente super le information que es disponibile a ille al tempore del examine.

Le natura e le circumstantias del tentativa de committer suicidio contine frequentemente indicios de valor in identificar le typo de agente usate e in determinar si o non le acto esseva deliberate. Un tentativa impulsive es frequentemente sequite per prompte expressiones de remorso, durante que le tentativa deliberate, ritualistic, e ben-preparate signala un plus serie intention.

Post le tentativa, mesuras immediate de urgentia, de reparo, e de resuscitation es indicate. In le majoritate del casos le patiente debe esser hospitalisate pro prevenir

le repetition del tentativa e pro render possibile le adequate evalutation psychiatric del causas subjacente. Le natura e le serietate del morbo subjacente, insimul con un consideration del factores precipitatori, determina le curso subsequente del therapia. Varie formas de therapia somatic—electrochoc, coma a insulina, o chimotherapia) es possibilemente necessari pro assister le patiente a superar le phase immediatemente critic de su morbo. Therapia a electrochoc ha le effecto quasi specific de elevar le depression. Le therapia debe visar a resolver le causas subjacente pro prevenir recidivas futur. Tractamento somatic o chimotherapia per se non pote effectuar un tal resolution. Tal mesuras adjuta in le restauration de un periodo temporari de equilibrio emotional, durante le qual le appropriate mesuras psychotherapeutic pote identificar le problemas fundamental.

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CLINICAL STAFF CONFERENCE

CRYPTOCOCCOSIS: CLINICAL STAFF CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH*

Moderator: NORMAN B. MCCULLOUGH, M.D. *Discussants:* DONALD B. LOURIA, M.D.,† T. F. HILBISH, M.D., LOUIS B. THOMAS, M.D., and CHESTER EMMONS, Ph.D., *Bethesda, Maryland*

DR. N. B. MCCULLOUGH: In our clinical research program on the granulomatous diseases we have studied 10 cases of cryptococcosis. We are taking this opportunity to present some of the clinical data, the pathology and epidemiology of the disease, the biology of the organism, and our results with experimental therapy. We have selected four cases that represent the span of the disease seen in our patients.

Dr. Donald Louria will present these cases.

DR. D. B. LOURIA: The first patient, J. C., represents disseminated cryptococcosis without central nervous system involvement.

Case 1. This Negro patient was 23 years old at the time of onset of illness, two years and nine months prior to his admission to the National Institutes of Health. He had been in the Armed Services, stationed first in Wyoming, later in California, and finally in Japan.

His illness commenced with night sweats and a nonproductive cough. Shortly thereafter he developed wheezing, exertional dyspnea, anorexia and fatigue, and lost 20 pounds in weight.

About a year after the onset of symptoms, which had persisted, a chest x-ray film was taken which revealed hilar lymphadenopathy and bilateral pulmonary infiltration. At this time he complained of pain in his left hip, although roentgen examination of the area revealed normal bony structures. Progressive swelling and tenderness of the left buttock developed, together with generalized peripheral lymphadenopathy. Biopsy examination of a lymph node revealed noncaseous granulomas, and a diagnosis of sarcoidosis was made.

He developed extremely severe low back pain, radiating down the legs, and a high fever. He was treated with cortisone, receiving up to 200 mg. daily over a prolonged period. His pain lessened, but the left buttock became more swollen, extremely tender and hot, and he continued to have fever. Sixteen months prior to admission he was transferred back to the United States, where the abscess in the buttock was drained; culture yielded *Cryptococcus neoformans*. The hilar lymph-

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adenopathy and bilateral pulmonary infiltration were still present. Roentgen examination also revealed an osteolytic lesion of the right anterior iliac spine. Laboratory examinations showed a white blood cell count and hemoglobin within the normal range, and an elevated serum globulin. The spinal fluid was examined several times and was found to be normal. A Kveim test was positive. Diagnoses of sarcoidosis and disseminated cryptococcosis were made.

The patient was treated intravenously with 2-hydroxystilbamidine daily for 33 days. During the course of therapy he developed a second abscess in the right thigh. He then received Mycostatin, 10,000 units daily intravenously for 60 days. He had marked chills and fever with these infusions. The lesions apparently healed and he improved markedly, but soon developed pain and swelling of his right wrist. At this time, because of its toxicity, Mycostatin for intravenous use was no longer available, and he was given amphotericin B orally, receiving 5 gm. daily for a period of four months. The swelling and pain in the wrist regressed. He was then referred to the NIH (July, 1956) for continued study and therapy.

On admission he appeared to be a fairly healthy man. The vital signs were normal. The parotid glands were markedly enlarged and firm, and there was a generalized lymphadenopathy. There were no abnormalities referable to the central nervous system. The white blood cell count, hemoglobin, liver function and urine were normal. The thymol turbidity was slightly elevated, and cephalin flocculation was 3 plus. The serum globulin was increased in amount, primarily in the gamma fraction. The spinal fluid was normal on several examinations. It was felt that he had disseminated cryptococcosis without central nervous system involvement. He was continued on oral amphotericin for an additional period of eight months. It was discontinued two months ago. He is clinically well.

Case 2. The second patient is C. R., a 52 year old white man. He had rheumatoid arthritis and rheumatic heart disease with increasing cardiac decompensation, and had been treated with digitalis. He also had had frequent, mild, generalized headaches. He had received prednisone, 20 mg. daily, for 16 months prior to admission.

Several weeks before admission he developed a different type of headache, which was very severe. His family noted a personality change, emotional lability, poor judgment, and irresponsibility in financial matters. Eight weeks prior to admission he displayed mental confusion and decreased responsiveness. The severity of his headaches had increased.

Five weeks before admission he had been admitted to another hospital. The main findings on physical examination there were a slightly stiff neck, a temperature of 104° F., and a tachycardia of 165 per minute. A lumbar puncture was done. The spinal fluid was under normal pressure; it contained 150 cells per cubic millimeter, 86% of which were lymphocytes; the protein content was 128 mg. and sugar, 17 mg. per 100 ml.; chloride, 109 mEq./L. It was felt that he had tuberculous meningitis, and antituberculous therapy was commenced. During the next four weeks he seemed to improve, then rapidly became worse, had hallucinations, and responded less readily. On the day before admission here a bilateral sixth nerve paresis was noted, and lumbar puncture revealed many cells of *Cryptococcus neoformans*.

On admission to the Clinical Center the patient was semicomatose, and had a temperature of 38.8° C., a heart rate of 100 per minute, and an irregular pulse and respiration. The blood pressure was 155/100 mm. of Hg. There were râles in both lung bases and a grade 2 apical systolic murmur. The neck was stiff; there were questionable bilateral papilledema, bilateral sixth nerve paresis, generalized hyperreflexia, bilateral extensor plantar responses, and monoplegia of the right leg. His mental status varied from stuporous to comatose. On the seventh day of hospitalization, while being prepared for cranial burr holes to relieve intracranial pressure, he

suddenly died. The ventricular fluid obtained at this time contained 1 polymorphonuclear leukocyte, 6 lymphocytes and 133 cells of *Cryptococcus neoformans* per cubic millimeter. The sugar content was 1 mg. and the protein 83 mg. per 100 ml.; chloride, 115 mEq./L. Necropsy revealed cryptococcal meningitis and a cryptococcal abscess in the right lung.

Case 3. The third patient, J. N., a 48 year old white man, became ill five years ago with sudden onset of severe headache and projectile vomiting. Lumbar puncture revealed a pleocytosis, a decreased sugar, and an increased protein content of the spinal fluid. Ventriculograms were normal. He improved and was discharged from the hospital. In retrospect, this may have been the beginning of his present illness. For the next four years the patient was asymptomatic. Nine months prior to admission a personality change was noted, manifested by nervousness, withdrawal and marked secretiveness. This status continued until four months prior to admission, when he developed many new symptoms, including ataxia, marked memory loss, mental confusion, verbal aphasia, and right-sided seizures without loss of consciousness.

He was admitted to a hospital in Missouri and studied extensively. Lumbar puncture again showed a pleocytosis, mostly of lymphocytes, a decreased sugar, and an increased protein content of the spinal fluid. The etiology was not established. He was transferred to the NIH for further evaluation.

On admission here his temperature was 37.2° C.; respirations, 12; pulse rate, 92 per minute; blood pressure, 138/90 mm. of Hg. He had a wide-based ataxic gait and a tendency to fall backwards with his eyes open. There were marked memory loss and difficulty in obeying even simple commands. The neck was supple. The cranial nerves functioned normally, and there was no papilledema. There was weakness of the flexors and extensors of the hips. Examination of the blood showed a normal hemogram, and the erythrocyte sedimentation rate was not increased. The results of liver and kidney function tests, electrolyte, and serum protein electrophoretic determinations were within the normal range. The urine contained occasional red blood cells. An intravenous pyelogram revealed a lesion, presumably inflammatory, in the right renal pelvis. Lumbar puncture was done; the spinal fluid was under normal pressure; it contained 91 white blood cells per cubic millimeter, of which 84 were lymphocytes; the sugar content was 8 mg. per 100 ml., and the chloride was normal in amount. *Cryptococcus neoformans* was recovered in culture from both the spinal fluid and the urine. This strain grew very slowly, requiring from four to six weeks to appear on Sabouraud's agar, and there was but one colony per milliliter of spinal fluid inoculated.

This patient has been treated with oral amphotericin, 3 to 5 gm. per day, for two months. There has been no change in his clinical condition or in the neurologic or spinal fluid findings.

Case 4. The fourth patient, D. J., is a 42 year old white woman who became ill three and one-half years ago. She had an acute onset of anorexia, nausea, vertigo, vomiting, occipital headache and tinnitus, and fever of moderate degree. She was admitted to another hospital and was found to have a slightly stiff neck. *Cryptococcus neoformans* was isolated from the spinal fluid. She received 2-hydroxystilbamidine for several weeks, and then sulfadiazine continuously until admitted here one year after the onset of illness. Her acute episode subsided and her disease has remained subacute, manifested by headache, fatigability and increasing visual difficulties.

The admission physical examination was normal except for bilateral papilledema of 4 diopters, and intermittent ventricular premature contractions. The results of laboratory examinations of the blood, including erythrocyte sedimentation rate, urine, and kidney and liver function tests, were all within normal limits. The spinal fluid

was under increased pressure and contained 60 cells per cubic millimeter, predominantly lymphocytes. The sugar content was 18 mg. and the protein 99 mg. per 100 ml. Roentgen examination of the skull and an electro-encephalogram revealed no abnormalities.

This patient has been hospitalized here nine times during the last two and one-half years. She has been extensively studied and has received numerous drugs. At present she is on oral amphotericin. During this period there has been no essential change in her clinical condition or in the results of laboratory studies. She complains of headaches and easy fatigability, but leads a reasonably normal sedentary life.

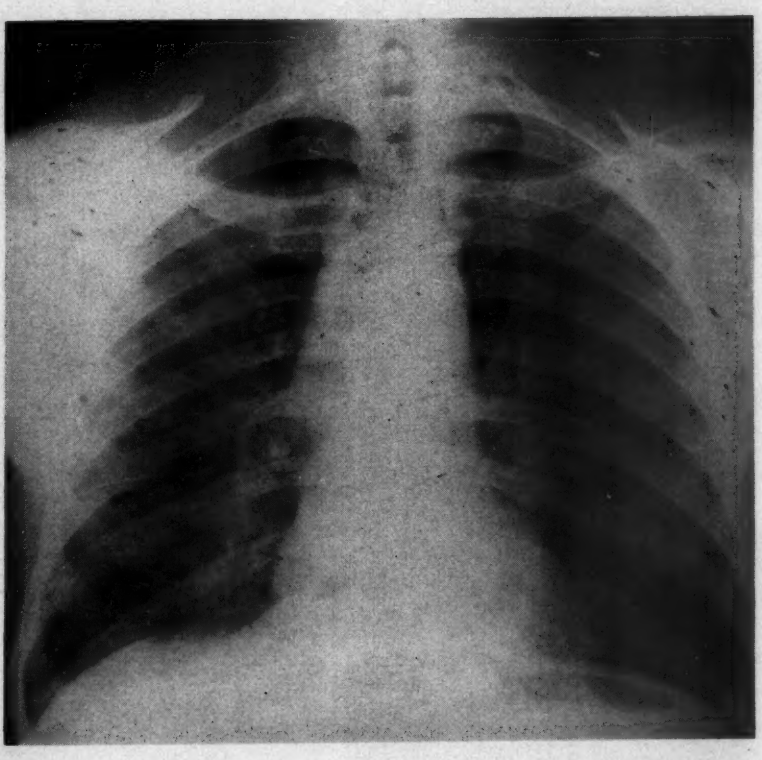

FIG. 1. Bilateral hilar adenopathy associated with fine disseminated pulmonary infiltrations.

Dr. Hilbish has some x-ray films to show you.

DR. T. F. HILBISH: A chest film of the first patient, J. C., demonstrates bilateral hilar adenopathy associated with fine disseminated pulmonary infiltrations, as shown in figure 1. Films of the right wrist and right femur reveal sharply circumscribed cystic lesions of the right radius and the distal end of the right femur (figure 2). Radiologically, these changes are not considered to be characteristic of cryptococcosis; in fact, the bony lesions are more suggestive of fibrous dysplasia, cartilaginous rests, or nonspecific cysts.

There are few references in the radiologic literature concerning cryptococcosis of the bone. It has been stated that bone involvement occurs in approximately 10% of patients with disseminated disease. The bony lesions present as cystlike areas of radiolucency, with a paucity of surrounding reaction. In this particular patient there were no symptoms referable to the distal femur, but a transitory swelling and redness of the right wrist had occurred. The x-ray findings are considered to be atypical for cryptococcosis, and we have no bacterial or histologic proof that the bony lesions were due to this disease entity.

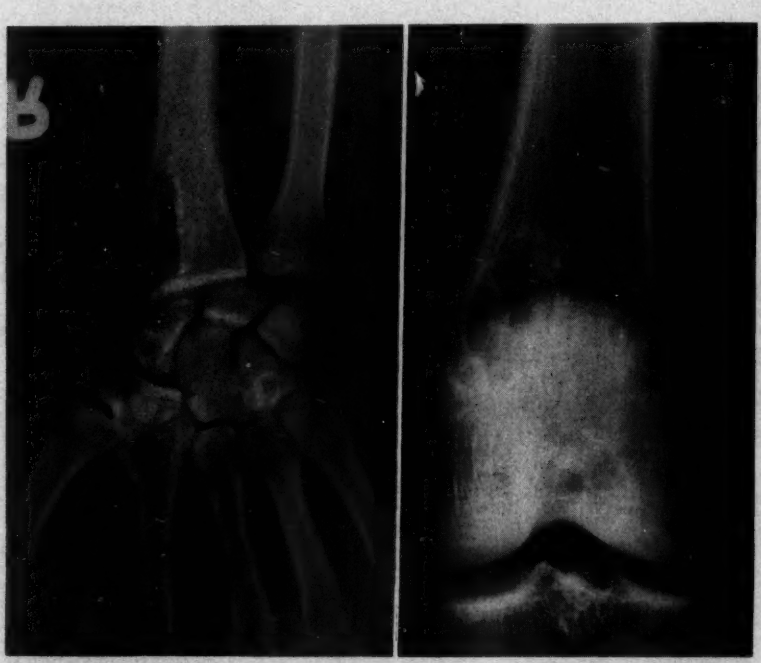

FIG. 2. Right wrist and right femur, showing sharply circumscribed cystic lesions, right radius and distal end.

The second patient, C. R., demonstrates a nodular type of infiltration in the right lung with cavitation, as shown in figure 3 and marked by an arrow. The films also show osteoporosis of the bony structures of the arms, especially of the right forearm. The findings are secondary to limitation of motion due to rheumatoid arthritis of the joints.

The pulmonary lesions of cryptococcosis are by no means pathognomonic. Dense consolidation may occur, or the changes may be patchy and disseminated. On occasion, isolated masses resembling peripheral neoplasms may be seen. Uncommonly, cavitation is observed, such as is demonstrated by this patient.

The third patient is J. N. An initial chest film in November, 1956, was negative except for the presence of an old healed Ghon complex. A portable

chest film on January 9, 1957, during a period of acute illness, shows extensive infiltration and a pleural effusion extending upward along the lateral chest wall (figure 4). Clinically and radiologically the findings were considered to be compatible with pulmonary infarction and pleural effusion. A subsequent film (January 18, 1957) reveals improvement, with reduction in effusion and pulmonary infiltration (figure 5). Eventually the chest findings resolved except for minimal residual fibrosis in the right lower lung field.

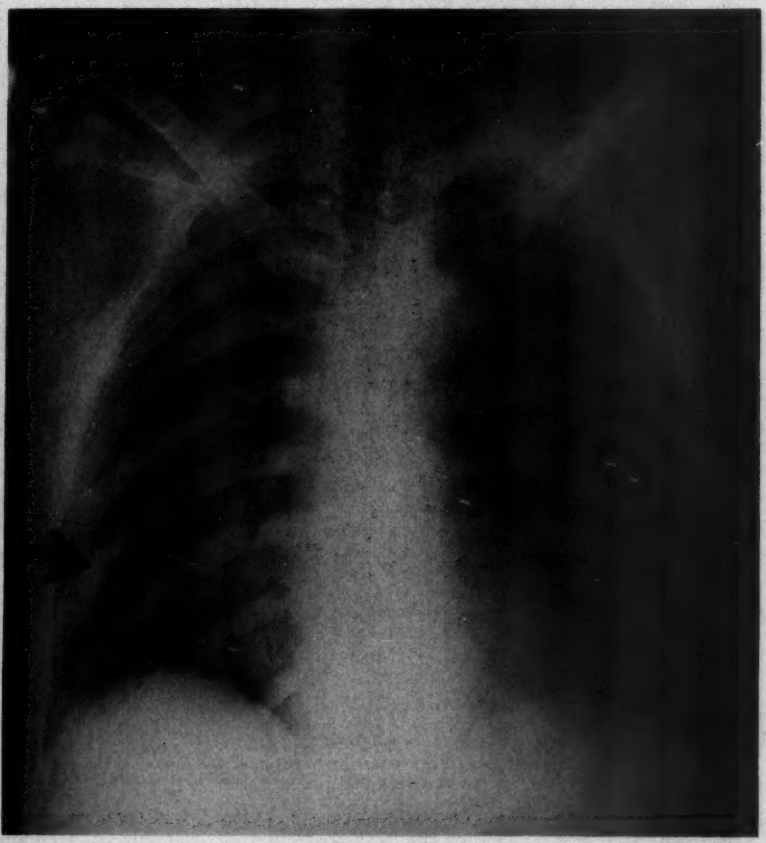

FIG. 3. Right lung, showing a nodular type of infiltration, with cavitation at the point indicated by arrow.

This patient also shows minimal changes consisting of blunting and dilation of the calyces, especially the right inferior calyces, as demonstrated by intravenous pyelogram. The changes were attributed to a cryptococcal infection, as the urine was positive for this organism.

The last patient, D. J., shows disseminated calcific deposits throughout both lung fields. These lesions were considered to be insignificant as far as crypto-

coccosis is concerned. They most likely represent an old healed histoplasma infection.

I would like to ask if this man had any clinical signs of joint difficulties at that time?

DR. D. B. LOURIA: He had rheumatoid arthritis and flexor deformities of his elbows.

DR. T. F. HILBISH: Were all of the changes confined to the joints per se?

DR. D. B. LOURIA: That is right. He had no other involvements.

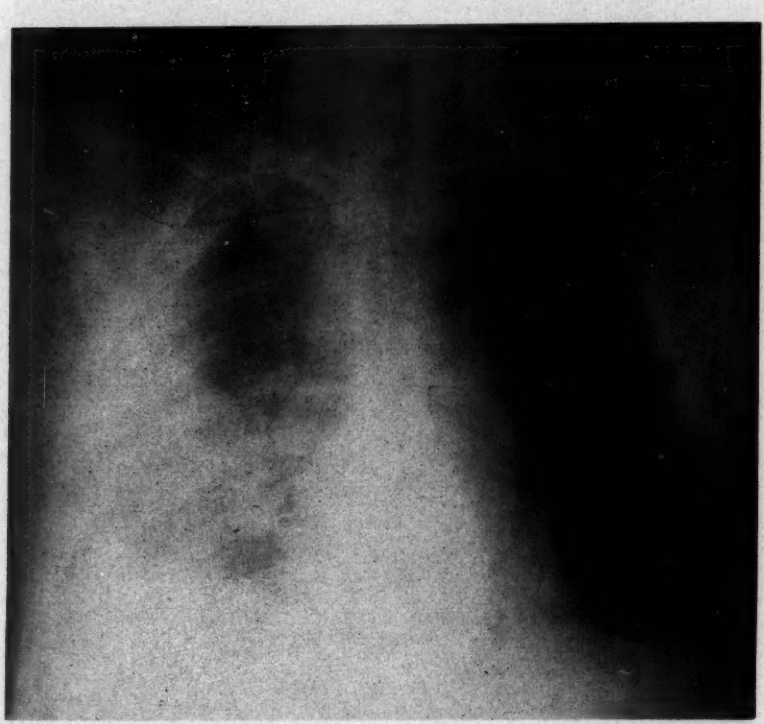

FIG. 4. Portable chest film, demonstrating pleural effusion and extensive parenchymal infiltration.

DR. T. F. HILBISH: I believe the best possibility is osteoporosis, secondary to the rheumatoid arthritis.

DR. N. B. MCCULLOUGH: The true incidence of cryptococcosis is unknown. Up to 1955 over 300 cases had been reported in the world literature. Currently, approximately 50 deaths from this disease are reported in the United States annually. Considering the frequency with which the diagnosis is made from the examination of surgical specimens and tissues removed at necropsy, we believe that this reported incidence is far too low, and that cryptococcosis may be a common disease.

The occurrence of pulmonary cryptococcosis without disease elsewhere in the body, together with the frequency of pulmonary lesions active or healed, in patients with cryptococcic meningitis and other disseminated forms of the disease, suggests that the lungs are the usual portal of entry of the organism. Probably in many cases, pulmonary infection remains entirely subclinical, or nearly so, with disease limited to a solitary lesion, or a few small lesions, which resolve without residual, or result in minimal scarring without calcification. Mildly symptomatic cases present with bronchitic symptoms, cough, scanty mucoid sputum, and low-grade fever. There may be occasional hemoptyses. Roentgen examination reveals one or more areas of infiltration, usually in the

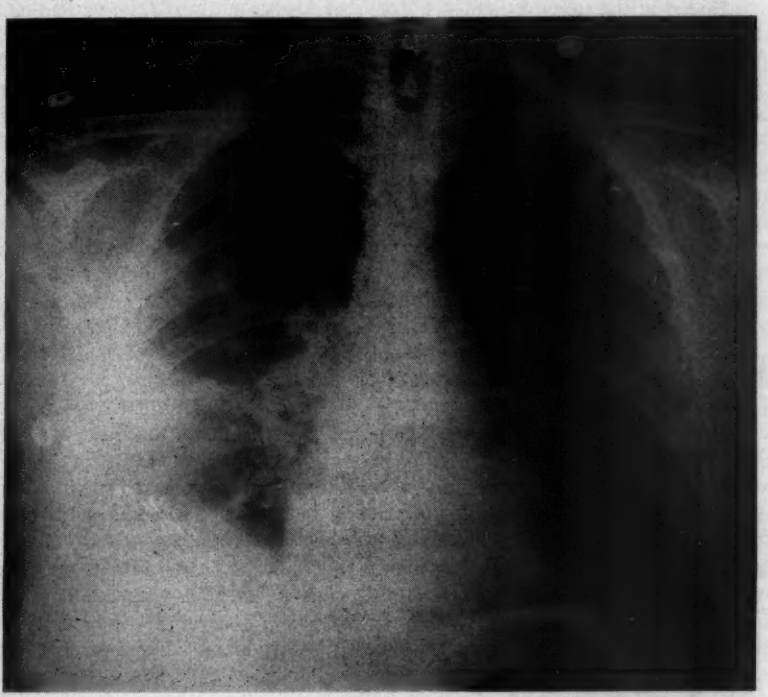

FIG. 5. Subsequent film, showing reduction in effusion and pulmonary infiltration.

lower half of the lung fields. In patients with more serious disease there are unilateral or bilateral areas of diffuse pulmonic infiltration or pneumonitis which may progress to extensive disease, which on roentgen examination may resemble tuberculosis in all respects. Cavitation seldom occurs. Hilar lymphadenopathy is absent or not conspicuous. Such lesions may heal after weeks or months, with minimal fibrosis and without calcification, or the infection may spread to other sites in the body. In general, pulmonary forms of the disease tend to have a benign course.

In disseminated disease, widespread miliary lesions of the lungs may occur which are radiologically indistinguishable from those of miliary tuberculosis.

The differential diagnosis of pulmonary cryptococcosis encompasses the group of slowly developing pulmonary diseases, namely, tuberculosis, other fungal diseases, sarcoidosis, chronic lung abscess, bronchiectasis, and neoplasms, primary or metastatic. The definitive diagnosis rests on isolation of the organism from the sputum, or from lung tissue obtained at necropsy, or by surgical excision.

About 10% of the cases in which the diagnosis of cryptococcosis is proved have pulmonary disease alone, or in association with other soft tissue lesions, exclusive of the central nervous system. In the remainder the central nervous system is primarily involved.

The onset of cryptococcic meningitis may be sudden or insidious. Both types are included in the cases presented today. In the acute disease the patient complains of rapidly developing, violent headache, vertigo, nausea and vomiting. The temperature is usually not as high as one would expect from the severity of the symptoms, although continued elevation to 104° F. or 105° F. is not uncommon. There are the usual signs of increased intracranial pressure, evidenced by papilledema, exudates, and hemorrhages in the retinae, and ocular palsies. Signs of meningeal irritation are almost always present. About two thirds of these cases end fatally in a few days or weeks. There is continued moderate-to-high fever, with signs of progressive increase in the intracranial pressure. The central nervous system manifestations may be multiple and varied. There may be many and scattered reflex changes, palsies, or even hemiplegia. The patient becomes somnolent, stuporous, comatose, and dies. Some few patients may exhibit wakefulness and signs of cerebral irritation, although this is unusual. A few may have localized or generalized convulsions. In patients not succumbing quickly there may be partial clinical remission of the disease, with lapse into a subacute or chronic form.

If the onset is gradual, the early symptoms are stiffness of the neck, headache, malaise and low-grade fever. Meningeal signs are usually present, but may be entirely absent for long periods in spite of the presence of marked pleocytosis in the spinal fluid. As the disease progresses, symptoms and signs of increased intracranial pressure develop and dominate the clinical course.

Whether the onset is gradual or abrupt, the usual case follows a progressively downhill course. Of the published cases, the majority of patients have died within six months, and 80 to 90% within a year. However, the clinical span of the disease may be quite variable. One of our patients is alive after five years and three months. We know of others who have lived for eight, nine or 10 years. The longest period of survival reported in the medical literature is 16 years. In such cases there may be clinical remission of symptoms for long periods. Most patients, however, continue to have complaints. Fifty per cent of cases at necropsy have widespread dissemination of the infection throughout the body. There are usually no gross lesions in the viscera, but there are multiple microscopic lesions throughout the liver, kidney, spleen, adrenals and other organs. Occasionally the clinical course is markedly influenced by secondary involvement of an organ, such as the adrenal, with the development of Addison's disease, or a kidney abscess. More usually the disseminated lesions do not grossly affect the clinical course or cause the death of the patient.

In 10% of the disseminated cases there are gross lesions in the bones. There is usually multiple involvement, the most common sites being the cranial bones,

which may become infected by direct extension from the sinuses, or the sella, the vertebrae, and the bony prominences of other bones. All bones have been reported to be involved. Infection seldom extends into a joint.

Skin lesions are also found in about 10% of these cases. They appear first as papules, often described as acneiform, which undergo necrosis, ulcerate, weep, crust and coalesce. Nodules and sinus tracts may occur. Occasionally there may be gross granulomatous masses. Probably all skin lesions are the result of dissemination of the infection, and the skin is probably seldom the portal of entry of the organism.

The differential diagnosis of cryptococcic meningo-encephalitis depends upon whether involvement is diffuse or localized, and includes most of the causes of meningitis, encephalitis, increased intracranial pressure, and pleocytosis in the spinal fluid. Other acute meningitides and encephalitides usually are soon differentiated without great difficulty. The disease most commonly confused with cryptococcic meningitis is tuberculous meningitis. The clinical aspects and spinal fluid findings are often very similar. The protracted cases of lymphocytic choriomeningitis likewise afford confusion. Perhaps the most difficult disease to differentiate from cryptococcic meningitis is sarcoidosis of the central nervous system without obvious lesions elsewhere. In cases with localized granuloma there are signs of an expanding intracranial lesion suggesting neoplasm, abscess or subdural hematoma. The spinal fluid may be normal, or the findings not suggestive of cryptococcosis. In such cases the diagnosis is usually not made until after neurosurgical intervention. Recovery of *Cryptococcus neoformans* from the spinal fluid establishes the diagnosis.

The white blood cell count is often normal, or only slightly elevated, but in terminal cases may be quite high. The erythrocyte sedimentation rate is usually elevated, and the blood serum globulin increased in amount. Spinal fluid examination reveals a pleocytosis, predominantly lymphocytic, a reduced sugar content, and an increased amount of protein.

The main diagnostic effort should be directed toward recovery of the organism by culture of blood, spinal fluid, bone marrow and urine, and injection of these materials into mice. Attempts to culture the organism are often unsuccessful in routine laboratory practice. Many of our cases are accepted for study on the basis of a presumptive clinical diagnosis, and are proved by culture of the organism after hospitalization here.

Dr. Louis B. Thomas will discuss the pathology of the disease.

Dr. Louis B. Thomas: The first two patients presented by Dr. Louria were included in a series of seven patients having cryptococcosis and whose lesions have been studied in the Department of Pathological Anatomy. No material for pathologic study is available from the other two patients he discussed. Both males and females may be infected, and the ages of these seven patients range from 2 to 50 years. Although involvement of the pulmonary and central nervous system is most common, lesions due to *Cryptococcus neoformans* may be found in many organs. One of the seven patients studied here was a two year old girl with cryptococcal meningo-encephalitis. Terminally there was dissemination of the organisms, and lesions were found in the lungs, spleen, liver and bone marrow.

Cryptococcosis is often a terminal infection in patients suffering from some other chronic disease. The first patient presented today had sarcoidosis, and

the second patient had rheumatic heart disease and arthritis. We have also seen cryptococcosis in a patient with metastatic carcinoma of the breast and in one with active pulmonary tuberculosis. Cryptococcosis has often been observed as a terminal infection in patients with malignant lymphoma.

The first two patients presented by Dr. Louria had involvement of the central nervous system. No photographs of the lesions in these two patients are available, but figures 6 and 7 illustrate the lesions found in the meninges and brain of another patient with cryptococcosis. In figure 6 the arachnoid is dull and opaque, due to yellowish white exudate in the subarachnoid spaces. Figure 7 shows the appearance of cryptococcal lesions in the brain substance. There are numerous,

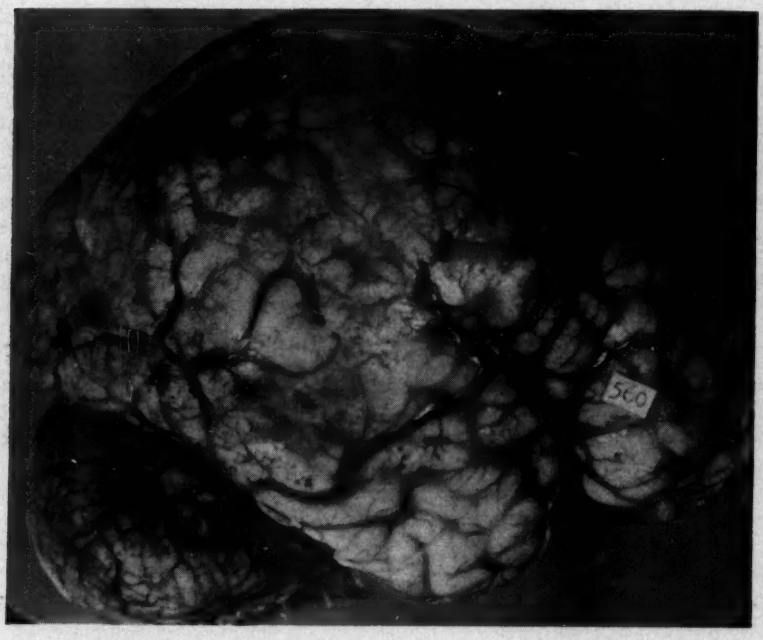

FIG. 6. Meningitis due to *Cryptococcus neoformans*. Exudate in subarachnoid spaces causes irregular opacity of arachnoid.

sharply circumscribed, glistening lesions in the basal ganglia, in adjacent white matter, and in the cortex. The lesions vary considerably in size. The glistening, gelatinous material of the capsules of the cryptococci produces the distinctive appearance of these lesions.

The cellular inflammatory response to cryptococci is quite variable. Infection of the meninges may occur with little or no cellular inflammation. Usually, however, the subarachnoid spaces are filled with variable numbers of polymorphonuclear leukocytes, lymphocytes, plasma cells and eosinophils. Such an inflammatory infiltrate is seen in figure 8, which shows an inflamed portion of the seventh nerve as it extends along the facial canal. Infection may extend

from the meninges to the cranial bones by following the cranial nerves, as illustrated in this photomicrograph. Occasionally the lesion may have some of the features of granulomatous inflammation. Figure 9 illustrates a focal collection of inflammatory cells and a large, multinucleated giant cell in the arachnoid of another patient with cryptococcosis. These variable types of inflammatory lesions may be seen in any organ or tissue when the infection is disseminated.

The second patient presented today had cryptococcal meningitis, but the most prominent lesions grossly were large, sharply circumscribed pulmonary abscesses. The largest abscess was 8 cm. in diameter and was filled with creamy,

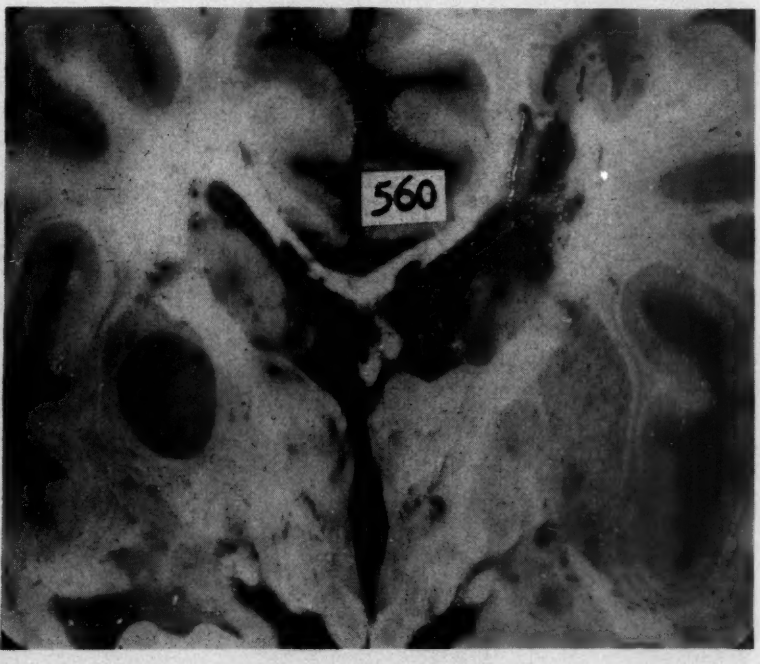

FIG. 7. Note gray, glistening lesions of variable size in both gray and white matter. These lesions contained myriads of cryptococci. The large lesion in the putamen measured over 1 cm. in diameter.

gelatinous material in which there were myriads of cryptococci. Many other abscesses, only 2 to 3 mm. in diameter, were found scattered throughout both lungs. Microscopically there were necrosis of pulmonary tissue and a mixed cellular exudate with fresh hemorrhage. Thus this patient exhibited massive pulmonary lesions caused by cryptococci. In another autopsy a single cryptococcal lesion which measured less than 1 cm. was found in one lung. This particular patient had breast cancer and terminally developed cryptococcal meningitis. It seems probable that this small lesion was the primary site of this patient's infection. Such a lesion could be missed duing examination of the lungs. This may

account for the fact that pulmonary lesions are not found in many patients with cryptococcal meningitis, although it is believed that the lung is the most frequent portal of entry.

In hematoxylin-eosin stained sections the organism is spherical and is surrounded by a clear halo. This halo, or unstained zone, is the gelatinous capsular

FIG. 8. Mixed inflammatory exudate in seventh cranial nerve. Petrous portion of temporal bone in lower half of photomicrograph. Hematoxylin-eosin stain.

material, and the amount of this material around each organism varies greatly. The organisms can be seen more distinctly in para-aminosalicylic acid or methenamine-silver preparations because part of the capsular material is stained (figure 10). Recently Dr. Igor Klatzo, of the Clinical Neuropathology Section,

has observed that the capsular material is brilliantly birefringent after staining a histologic section with cresyl violet. These special stains are quite useful to the pathologist in examining histologic sections for cryptococci.

DR. N. B. MCCULLOUGH: The next speaker is Dr. Chester W. Emmons. We are fortunate in that Dr. Emmons, an outstanding medical mycologist, is

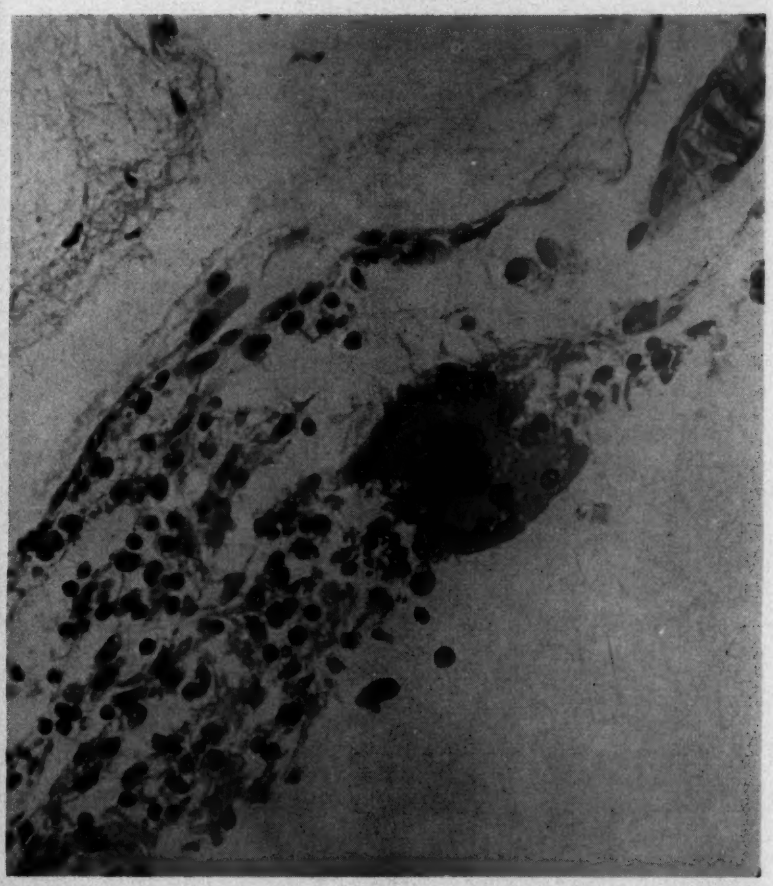

FIG. 9. Photomicrograph of focal area meningitis due to cryptococci. Note multinucleated giant cell. Hematoxylin-eosin stain.

available not only to advise us but also to collaborate with us in our research projects.

DR. C. W. EMMONS: My comments do not relate to the specific case reports that you have heard here today, but rather consist of a few general observations which I will preface by a short definition. Cryptococcosis is a noncontagious mycosis with a predilection for the central nervous system. It is caused by

Cryptococcus neoformans, a spherical, budding yeast with a wide, extracellular polysaccharide capsule. I give this definition because all the items are pertinent to an understanding of cryptococcosis. The spherical shape is important, because it helps in the histologic and culture diagnosis of the condition. Most

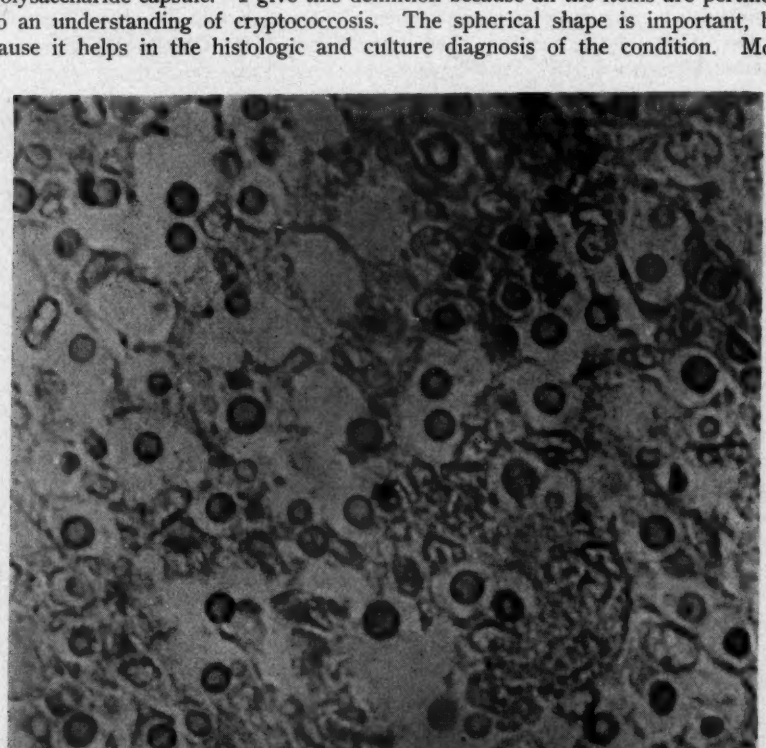

FIG. 10. Photomicrograph showing spherical form of cryptococci. The gelatinous capsular material forms a clear zone around each microörganism. Bauer stain.

yeasts are egg-shaped or elliptic in outline. This fungus, as you saw in the very beautiful slide which Dr. Thomas has shown, is usually spherical.

The last point in the definition, the encapsulation, is equally important. I have finally accepted the fact that my friends in pathology and I usually mean something different when we speak about a capsule. For example, when Dr.

Darling described histoplasmosis he was speaking of a protozoon. The most remarkable feature of the etiologic agent from that viewpoint was that this organism had a more or less rigid exterior wall. He therefore named it *Histoplasma capsulatum*. We have been arguing ever since, rather futilely, as to whether histoplasma has a capsule.

The mycologist speaks of a capsule in the bacteriologic sense, meaning a slimy or gelatinous material on the outside of a cell wall. The capsule of *C. neoformans* has been studied rather extensively because of its importance in the biology and the identification of the fungus and in the serology of the disease it causes.

According to Einbinder, Benham and Nelson, who studied the fungus in 1954, the capsule is composed of hexuronic acid, 6.7%, expressed as glucuronic acid; hexose, 18.1%, expressed as glucose; and pentose, 31.0%, expressed as arabinose. Other studies by other investigators more or less confirmed this.

There has been a difference of opinion as to whether hyaluronate is present. Drouhet in Paris has stated that hyaluronidase dissolves the capsule. Other investigators have not been able to confirm this. The capsule is of more than academic and chemical interest. It is generally considered that weakly encapsulated strains are less antigenic than are those with thick capsules. Yet the capsule itself is antigenic. Evans in particular has made extensive study of this material and has proposed a division of the species into three types, based upon the capsular material.

One interesting phenomenon that has been observed is a very sharp visualization of the outside of the capsule when the cells are suspended in antiserum prepared against that particular strain. This, to a considerable extent, is a type-specific reaction, although there is some crossing which can be prevented by absorption.

Besides its possession of a wide capsule, *C. neoformans* differs from other yeasts in that it is less active biochemically than are many of the yeasts. No gas is produced in any sugar, acid is produced slowly and rather erratically in a number of sugars, and gelatin is liquefied very slowly or not at all.

We had the opportunity a few years ago of studying the extent of variation within the species by examination of a large number of strains isolated over a short period of time from an outbreak of bovine mastitis. Presumably all of the infections came from one strain, since there was evidence that this infection was transmitted from one animal to another by the mechanical milker used. In the study of 62 strains from these cattle, all 62 produced acid rather slowly in glucose, levulose and mannose. Fifty produced acid in sucrose, 24 in maltose, 19 in starch, and none in galactose. All were virulent for mice.

This is the pattern of variation that occurs when one compares strains from other sources as well: strains from human cases, or strains isolated from soil.

This matter of variation is one that is quite important and certainly merits further study. Dr. Louria is making some studies of this point at the present time. I believe further critical studies must be made to elucidate some of the problems associated with clinical variation and other problems of cryptococcosis. There is variation in the amount of encapsulation, in the color (varying from white to tan), in the size of the cell, in the pathogenicity for mice, and in the ability to grow at higher temperatures.

One of the important problems in the epidemiology of cryptococcosis which

has not yet been fully solved is the source of infection. Like most of the deep mycoses, cryptococcosis is not contagious. Cases appear sporadically in both man and animals. Many species of animals are susceptible, including the horse, dog, cat, cow, cheetah, fox, civet, monkey, guinea pig and ferret. There is no evidence, however, that these animals are important reservoirs of infection from which man is infected, or that the disease is spread from animal to animal or from man to man. On the contrary, all the evidence, as in other deep mycoses, points to a saprophytic existence, independent of human or animal infection.

The fungus has long been known—since its first description, in fact—to have a saprophytic occurrence in nature. In 1894, Sanfelice isolated a fungus from a peach and showed it to be pathogenic in guinea pigs. Since that time, only sporadic cases in man and animals and a few isolations from milk had been reported until 1951 when, more or less by accident, I isolated Cryptococcus from soil. The first isolations were few in number and showed no particular pattern of distribution, but in later studies we found a very remarkable association with the pigeon. In one series, in which we deliberately looked for the organism in old pigeon nests and droppings, we isolated the fungus from 63 of 111 specimens collected on 19 different premises. The isolations were made from 16 of these 19 premises.

This relationship to the pigeon may exist because of the pigeon's nesting habits. The pigeon's nest is never cleaned from the time it is first built in the spring until the end of summer, during which period several broods are usually raised. At some time apparently during this nesting season, the nest and the droppings underneath the roosting places are seeded with Cryptococcus. The fungus is able to grow in this environment.

We have made an attempt to isolate the fungus from pigeons, so far without success. We assume what would appear to be obvious, that the pigeon probably eats contaminated fruits or seed at some time, and that the fungus passes uneventfully through the gastrointestinal tract and grows as a saprophyte in the droppings. This is not only interesting because it represents an unusual habitat, but it is of epidemiologic importance because there have been several outbreaks of pneumonitis in persons exposed to pigeon droppings—people who have cleaned out old attics or partially demolished buildings where pigeons have nested.

There was one epidemic in Cincinnati, diagnosed as histoplasmosis by serology, which stemmed from an old water tower where the men involved in cleaning this building developed pneumonitis. In most outbreaks of pneumonitis of this type the diagnosis has been ornithosis, or, when that has been ruled out, histoplasmosis. The diagnosis of cryptococcosis has not been considered in the past. However, it certainly must be in the future. The occurrence of a primary pulmonary lesion in some cases has already been discussed. The inhalation of dust from contaminated sources would seem to be a probable route of infection.

DR. N. B. MCCULLOUGH: The last presentation is by Dr. Donald Louria, who will review some of the results obtained in experimental therapy of the disease.

DR. D. B. LOURIA: The treatment of disseminated cryptococcosis in the past has been extremely disappointing. There has been a report of an apparent cure with sulfonamides, and several other patients have been at least temporarily

improved with sulfonamides. Similarly, several patients have benefited from cyclohexamide (Acti-dione) therapy. One patient with disseminated cryptococcosis not involving the nervous system improved dramatically following the administration of 2-hydroxystilbamidine. Excellent results were obtained in another patient with intravenous Mycostatin. The intravenous preparation of Mycostatin, however, had impressive toxicity and now is no longer available. In the majority of patients, therapy with sulfonamides, cyclohexamide, hydroxystilbamidine and a number of other drugs has been of no benefit.

We have been interested in amphotericin B, an antibiotic isolated from an unnamed streptomyces. Its structure has not yet been established. We have tested amphotericin B against 14 strains of *C. neoformans* in the test tube, using a conventional serial dilution technic. All strains were inhibited by between 0.03 and 0.12 μg/ml. of amphotericin B. It was found, however, that even in concentrations of 5 μg/ml. the drug was fungistatic and not fungicidal.

Mice were inoculated intravenously with 2,500,000 cells of a 24-hour culture of *C. neoformans*. This inoculation produced an overwhelming pneumonia in a few of the animals in each group, with death in 48 hours. The rest of the animals developed hydrocephalus and died within seven to 21 days. This laboratory model seems to be fairly similar to some of the human cases of overwhelming disseminated cryptococcosis. Amphotericin B was administered using various dosage regimens starting one day after infection. Either 25 or 50 mg./Kg./day were administered intraperitoneally, or 15 or 150 mg./Kg./day were given orally. The oral dosage is only an estimation, since the form of the antibiotic was not soluble and was given in suspension in the drinking water. An occasional animal in the treated group died within 48 hours from overwhelming cryptococcal pneumonia. Thereafter, while on treatment for 25 days, a negligible mortality occurred on any of the treatment regimens.

The animals were then allowed to survive for 14 days after treatment was stopped and were then sacrificed. The brains were cultured on Sabouraud's agar and all cultures were held for 30 days before being considered to be negative.

On the low intraperitoneal dosage (25 mg./Kg./day) and the low oral dosage (15 mg./Kg./day), despite the fact these animals were protected from death, all yielded positive cultures at autopsy. Animals treated with 50 mg/Kg./day intraperitoneally also all gave positive cultures. However, a marked decrease in the number of colonies per slant was noted.

With the higher oral dosage of approximately 150 mg./kg./day, one third to two thirds of the animals, depending upon the group, were culturally negative.

Blood levels of amphotericin were determined on the various dosage regimens by a bio-assay technic. These were compared to levels found in humans on oral dosage of up to 5 gm. per day. Absorption is poor after oral administration, and the maximal level obtained in man is 0.25 μg/ml., which is just above the fungistatic level in vitro. Animals with similar blood levels of the drug were not cured. Those groups in which, after treatment, one third and two thirds of the animals were culturally negative had blood levels between 0.80 μg/ml. and 1.50 μg/ml., about six times that found in humans receiving oral amphotericin.

We have treated a group of six patients with cryptococcosis with oral amphotericin in dosages of up to 5 gm. per day. One of these patients showed no improvement. Three, including two with chronic meningitis and one with

disseminated disease without central nervous system involvement, showed distinct symptomatic improvement in terms of alleviation of such symptoms as headache, malaise and fatigue. However, spinal fluid cultures remained positive, and derangements in cell count, protein and sugar concentrations were not altered.

The other two patients had cryptococcal involvement of the central nervous system and also evidence of disease of the liver and/or the kidneys. There was no objective evidence of improvement in the central nervous system involvement. However, there was apparent resolution of the hepatic and renal disease. It appears from this study that oral amphotericin was beneficial in treating infections not involving the nervous system. Subjective but no objective improvement was noted in patients with central nervous system involvement. The failure of central nervous system disease to respond to oral amphotericin may be related to the small concentrations of the drug which diffuse into the cerebrospinal fluid from the blood. Thus with a blood level of 0.25 μg/ml., the maximal cerebrospinal fluid level achieved in these patients was 0.015 μg/ml., which is below the in vitro fungistatic level.

We have treated two patients with cryptococcosis with intravenous amphotericin. At a dosage of 30 mg. daily, the peak blood level attained was 3 μg/ml., at which time the spinal fluid level was 0.09 μg/ml., just equal to the concentration required for in vitro fungistasis. Neither patient has shown objective improvement thus far.

In view of our experimental and clinical data, it appears to us that oral amphotericin will be of some benefit in cryptococcal disease outside the central nervous system, but will be of little value in patients with central nervous system involvement. Intravenous amphotericin may be expected to be highly beneficial in some patients with disseminated cryptococcosis. It is obviously much too early to predict what proportion of patients with central nervous system involvement will be significantly improved.

Summario in Interlingua

Le conferentia esseva concernite con le thema de cryptococcosis. Illo consisteva del presentation de historias de casos illustrante le phases clinic del morbo e de discussiones del examines roentgenologic effectuate in ille patientes, del aspectos clinic e del diagnose differential del morbo, del signification de materiales pathologic ab le casos presentate, del pathologia del morbo in general, del biologia de *Cryptococcus neoformans* e del presumite epidemiologia del morbo, e del resultatos de therapia experimental in animales e humanos.

Le ver incidentia de cryptococcosis non es cognoscite. Usque 1955, plus que 300 casos esseva reportate in le litteratura medical del mundo. Viste le frequentia de diagnoses effectuate super le base del examine de specimens chirurgic o necroptic, il es possible que cryptococcosis es un morbo commun.

Il es probabile que le pulmones es le usual porta de penetration pro le organismo. Le diagnose differential de cryptococcosis pulmonar presta attention al gruppo de morbos pulmonar que se distingue per lor lente disveloppamento, i.e. tuberculose, altere morbos fungal, sarcoidosis, chronic abscessos pulmonar, bronchiectasis, e neoplasmas (primari o metastatic).

Le diagnose differential de meningo-encephalitis cryptococcic depende de si le affection es diffuse o localisate. Illo include le majoritate del causas de meningitis, encephalitis, augmento del pression intracranial, e pleocytosis in le fluido spinal. Le

formas acute de meningitis e de encephalitis es usualmente differentiate sin grande difficultate. Le morbo confundite le plus communmente con meningitis cryptococcic es meningitis tuberculotic. Casos de prolongate choriomeningitis lymphatic es equalmente apte a causar confusion. Sarcoidosis del systema nervose central sin obvie lesiones in altere partes es forsan le morbo le plus difficile a differentiar ab meningitis cryptococcic.

In omne formas de morbo cryptococcic, le diagnose definitive depende del identification de *C. neoformans* in specimens prendite ab le patiente.

Cryptococcosis es frequentemente un infection terminal in patientes qui suffre de un altere morbo chronic. Illo ha frequentemente essite incontrate in patientes con lymphoma maligne.

In experimentos con muses, amphotericina B se monstrava promittente como droga therapeutic. Sex patientes esseva tractate con iste agente, administrate per via oral. Le droga, assi administrate, pareva esser benefic in infectiones que non afficeva le systema nervose central. Le absorption del droga non es bon. Le nivello maximal de illo in le sanguine, obtenite per dosages diurne de usque a 5 g, esseva 0,25 μg per ml. Le correspondente nivello maximal in le fluido cerebrospinal esseva 0,015 μg per ml. Iste valor es infra le nivello fungistatic in vitro.

Duo patientes esseva tractate con amphotericina in administration intravenose. Un dosage diurne de 30 mg resultava in un nivello maximal de 3 μg per ml in le sanguine e de 0,09 μg per ml in le fluido spinal. Ambe patientes remaneva sin melioration objective.

Iste resultatos suggere le conclusion que amphotericina in administration oral es possibilimente de beneficio in morbo cryptococcic extra le systema nervose central, sed quando le systema nervose central es afficite, le beneficio del droga es plus tosto negligible o non-existente. In administration intravenose, le droga pote esser multo benefic in cryptococcosis disseminate e es possibilemente etiam de un certe valor in patientes in qui le morbo ha afficite le systema nervose central.

CASE REPORTS

ANAPHYLACTOID REACTION TO ORAL PENICILLIN: REPORT OF A CASE*

By Frank J. Martin, M.D., *Ada, Oklahoma*

The specter of penicillin reactions, both mild and severe, faces the physician who chooses to use penicillin in his armamentarium of treatment. The first case of anaphylactoid shock developing from intramuscular penicillin was reported in 1945.[1] The initial cases of anaphylaxis to oral penicillin were noted in 1953.[2, 3, 4] Maganzini,[5] in his recent brief review of the literature, found 13 cases of anaphylactic shock due to oral penicillin. In his report he added two more to the literature. One case was due to penicillin V (phenoxymethyl penicillin), the other was attributed to penicillin G administered by mouth. Since then Gullatt[6] has reported one additional case of anaphylactic shock from a penicillin lozenge containing 50,000 units of penicillin G. The case below illustrates a severe anaphylactoid reaction to an oral penicillin G (50,000 unit) tablet.

Case Report

This 52 year old woman was seen in the emergency room at the hospital at 12:30 p.m. on October 26, 1957. The only history obtainable was that the patient had bought some penicillin tablets at a drug store for a cold, had taken one, and in a matter of 30 seconds had a feeling of suffocation in the neck and upper chest and collapsed. She was brought to the emergency room in profound shock. Another physician who happened to be there at the time saw her, started levarterenol, and gave her 100 mg. of Demerol. She was seen by me shortly after that. No radial pulse or blood pressure was obtainable. Another ampule of levarterenol was added to the infusion solution. Blood pressure an hour later was 100 mg. Hg systolic. She was given Neopavrine, 8 c.c. intravenously, because of a wheezing in her chest. Solu-Cortef, 100 mg., was administered intravenously, as was Coramine, five ampules intravenously. Five milligrams of Nalline were given because of her respiratory depression. In about two hours her blood pressure was stabilized.

Physical examination showed a cyanotic, acutely and critically ill female. Eye, ear, nose and throat examination was negative. Auscultation revealed wheezes in the chest. The blood pressure was not obtainable at first. The heart tones were rather distant; the rate was 120 at the apex. The abdomen was tender. There was no tenderness or swelling in the extremities.

An electrocardiogram obtained when she was in profound shock showed S-waves in Leads 2 and 3, a depressed SST in aVF, and depressed SST in $V_{4, 5 \text{ and } 6}$.

The initial blood count, obtained while the patient was in shock, showed a hemoglobin of 17.3 gm.% (112%); hematocrit, 55 vol.%; white blood cells, 15,350, with

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12 stabs, 55 seg., 77 polymorphonuclears, 21 lymphocytes and 4 monocytes. The prothrombin time was 100%. The serum transaminase was 14 units.

An electrocardiogram at 5:00 p.m. the same day showed an elevation of the SST segments that had been depressed. In aVR there was depression of SST; SST was elevated in $V_{2, 3, 4, 5 \text{ and } 6}$.

A day later the electrocardiogram was within normal limits. The hematocrit was approaching normal (48 vol.%). The white count was 14,000. The differential was: eosinophils, 1; stabs, 5; segs, 63; lymphocytes, 22; monocytes, 2. Hemoglobin was 99% (15.3 gm.%). Coagulation time was four minutes; bleeding time, one minute.

The levarterenol was discontinued the next morning after the patient's blood pressure had stabilized at 120/80 mm. of Hg. There was beginning infiltration at the site of the infusion. This had to be given in a small vein in the forearm because no other veins could be found at the time. The pain in the forearm the next day was thought to be on the basis of vasospasm produced by the infiltration of levarterenol.

The patient continued to complain of postnuchal headache on the fourth day of hospitalization, but was doing well otherwise. She was discharged from the hospital eight days after admission.

The history indicated that the patient had had many doses of Crysticillin for various things in the past. In 1952 she had suffered an urticarial reaction after having had 10,000 units of estrogen in oil. In 1949 she had been given 2 c.c. of concentrated liver extract and 300,000 units of Crysticillin simultaneously, intramuscularly, and had developed an urticarial reaction following these injections. It was then thought to be due to the liver. She was given Benadryl and adrenalin in oil and made an uneventful recovery. Other medical diseases in the past were rheumatism of a nonspecific type, anemia, nervousness, and ileitis since 1954. In 1948 she had had a cholecystectomy and an appendectomy. In 1956 she had had an anterior colporrhaphy and hemorrhoidectomy.

Discussion

It became apparent from this case and from those studied of a similar nature that penicillin anaphylaxis, both orally and parenterally administered, should be considered in every patient seen in shock. The differential diagnosis may be clarified only after the patient is brought back from impending death. The treatment of this condition depends heavily upon the use of adrenalin, noradrenalin, hydrocortisone, oxygen and other supportive measures.

An enzyme, penicillinase, recently introduced, has proved very effective in treating allergic reactions to penicillin. This is accomplished by the most logical approach: the drug completely inactivates the inciting antigen in a very short time. Penicillinase is considered the treatment of choice for the delayed serum sickness type of reaction. It is doubtful that this form of therapy will play an integral part in the treatment of anaphylactoid reactions to penicillin.

It has been shown that prophylactic use of antihistamines does not alter appreciably the susceptibility to penicillin reactions.[7] Penicillin anaphylaxis occurring in a patient on steroid therapy has been reported recently.[8]

The penicillin sensitivity problem therefore becomes one of great importance. It is well known that patients who have previously shown allergic manifestations, those with atopic dermatitis and asthma, are prone to develop the more serious reactions. There are insufficient data to evaluate completely the skin scratch

and conjunctival tests. A severe anaphylactoid reaction has been reported following use of the conjunctival test in a person who had previously developed a skin rash secondary to penicillin.[9]

In addition to the above tests, prior to administration of parenteral penicillin, a "tongue" or buccal test for anaphylactic sensitivity to oral penicillin is being used. An uncoated penicillin tablet is applied briefly to the tongue or buccal mucosa. If no local or systemic reaction occurs within 15 minutes, full oral doses of penicillin are administered. Again, data are insufficient to offer an evaluation of the method.[10]

The sensitivity tests are therefore not without danger, and do not always predict the extreme response. It does appear logical to assume that it would be better to test the individual rather than to give him an uncontrolled, full therapeutic dose. Since drugs do not prevent penicillin reactions, and sensitivity tests are not predictable, it seems that the best preventive is its use only when absolutely indicated.

Summario in Interlingua

Le medico qui utilisa penicillina in le tractamento de su patientes debe expectar le occurrentia de reactiones de leve grados e etiam de grados sever. Anaphylaxis ab penicillina parenteral esseva primo reportate in 1945. Le prime casos de anaphylaxis ab penicillina oral esseva reportate in 1953. Depost ille tempore, 16 casos de reaction anaphylactoide a penicillina oral ha essite reportate in le litteratura.

Le caso reportate in le presente articulo esseva causate per le ingestion de un tabletta de 50.000 unitates de penicillina G. Le patiente esseva un femina de racia blanc de 52 annos de etate. Illa collabeva intra 30 secundas post le ingestion del droga. Illa esseva tractate con levarterenol, Neopavrina, Solu-Cortef, Coramina, Demerol, e Nallina e oxygeno. Le pression de sanguine e altere responsas se renormalisava intra tres horas. Le hemoconcentration e le configuration electrocardiographic redeveniva normal intra 24 horas. Le patiente esseva dimittite ab le hospital post octo dies. Le historia passate de illa includeva reactiones urticarial que habeva occurrite a duo occasiones post administrationes de extracto hepatic, estrogeno in oleo, e Crysticillina. Iste reactiones habeva essite tractate, a bon successo, con adrenalina e Benadryl.

Le possibilitate de anaphylaxis ab penicillina debe esser prendite in consideration in omne patiente presentate in stato de choc. Le tractamento de iste condition require urgentemente le immediate uso de adrenalina, noradrenalina, hydrocortisona, e oxygeno. Le varie tests que pote esser usate ante le therapia non predice necessarimente le occurrentia de un responsa extreme. Il ha essite demonstrate que le uso prophylactic de antihistaminas non altera appreciabilemente le susceptibilitate del patiente de disveloppar reactiones a penicillina. Anaphylaxis ha occurite in un patiente qui recipeva simultaneemente un therapia a steroide. Il ha essite constatate que patientes, qui ha previemente exhibite manifestationes allergic o qui ha dermatitis atopic e asthma, es le plus serie reactores.

Il es sage, evidentemente, testar le patiente ante que ille recipe un complete dose therapeutic. Tamen, le melior methodo pro prevenir reactiones anaphylactoide a penicillina es usar le droga solmente quando illo es absolutemente indicate.

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PULMONARY INFILTRATION WITH EOSINOPHILIA (LÖFFLER'S SYNDROME) DUE TO SMOKE INHALATION: REPORT OF A CASE AND COMMENT ON PATHOGENESIS *

By William Tschumy, Jr., M.D., *Dallas, Texas*

Recent reviews [1, 2, 3] have emphasized the numerous and varied agents which may be responsible for the clinical syndrome of pulmonary infiltration with peripheral blood eosinophilia. It has become increasingly apparent that, in spite of the multiple causes, the basic pathogenesis probably represents a hypersensitivity reaction to various antigens to which the pulmonary tissues may be exposed. A review of the literature has failed to reveal a previously reported case following inhalation of smoke fumes. The present case demonstrates certain features suggesting a delayed allergic inflammatory reaction in the pulmonary interstitial tissues.

Case Report

A 40 year old white fireman complained of chest tightness, weakness, shortness of breath and increasing unproductive cough of two weeks' duration. While fighting a fire in a fabric and upholstery store four weeks prior to his initial visit he was overcome by smoke, which resulted in paroxysmal coughing, chest tightness, weakness and nausea. He was given oxygen and by the following morning was asymptomatic except for slight weakness. He returned to work and felt entirely well for

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two weeks, after which the development of a progressive cough and chest tightness prompted him to have a chest microfilm taken. This x-ray was negative. His symptoms gradually increased and were accompanied by weakness, ease of fatigue and exertional dyspnea. Fever, chills, chest pain or other constitutional symptoms were absent. There was no past history of pulmonary symptoms, or of exposure to infectious diseases or sick fowl. Significant travel history could not be elicited. There was no allergic background.

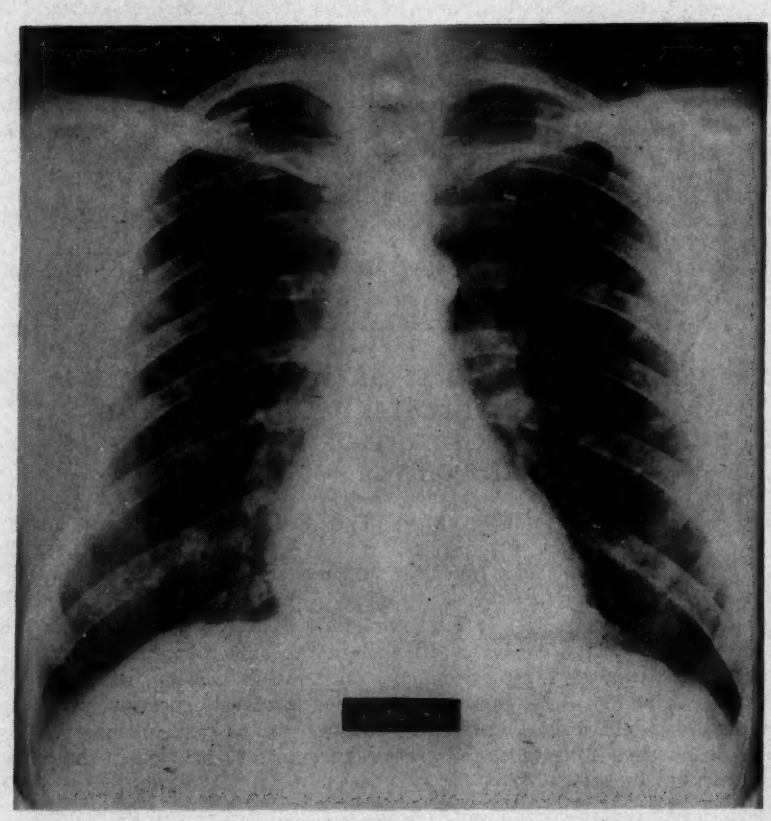

FIG. 1. Chest x-ray four weeks after smoke exposure and two weeks after onset of symptoms. Widespread patchy infiltrates are noted throughout both lung fields, and obliteration of the right costophrenic angle is present.

Physical examination was entirely negative. The temperature was normal, the pulse was 88, respirations 20. The blood pressure was 125 systolic, 85 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.2 gm. per 100 ml., and a white cell count of 12,400, with 63% neutrophils and 8% eosinophils. The sedimentation rate (Westergren) was 11 mm. in 60 minutes. Total serum protein was 6.05 gm. per 100 ml.; albumin, 3.80, and globulin, 2.25 gm. per 100 ml. Cold agglutinins were absent. Sputum was not obtainable for examination. A chest x-ray (figure 1) showed widespread, patchy infiltration throughout

both lungs but sparing the apices. The right costophrenic angle was obliterated, and the hilar vascular markings were slightly exaggerated, without hilar or mediastinal adenopathy. Intradermal skin tests were positive with histoplasmin and tuberculin, negative with coccidioidin. The blood serum showed negative complement-fixation tests for influenza A and B, Q fever, and members of the psittacosis-lymphogranuloma venereum group. Complement fixation tests for histoplasmosis and coccidioidomycosis were negative. Stool examinations for ova and parasites were negative. The electrocardiogram was normal.

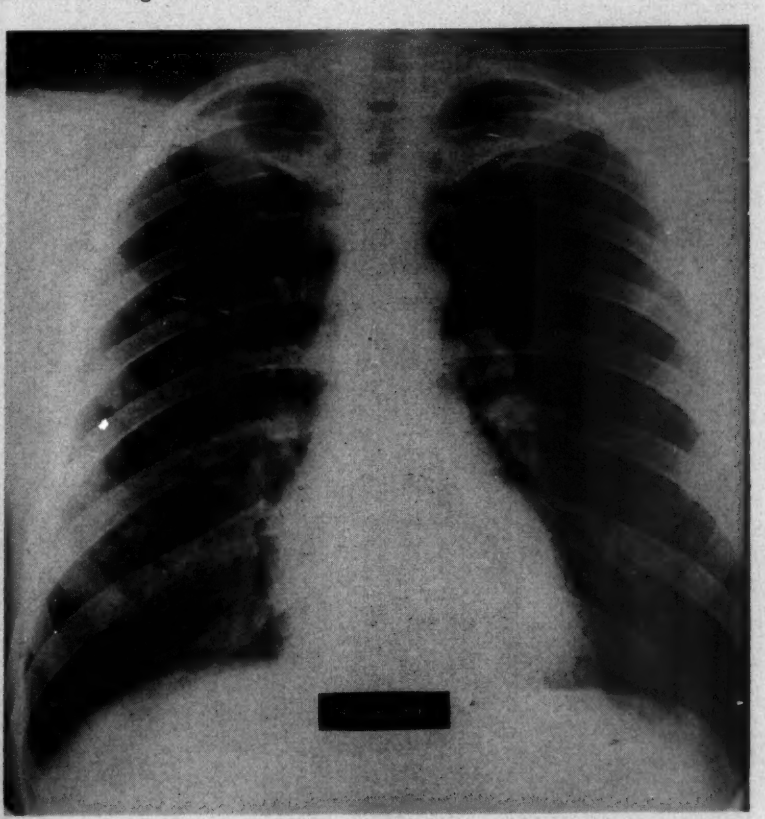

FIG. 2. Chest x-ray five weeks after exposure to smoke shows decrease in size of pulmonary infiltrates, which have become miliary in type. The right costophrenic angle has cleared.

During the following week in the hospital the patient's cough, chest tightness, exertional dyspnea and weakness improved slightly. He remained afebrile and without abnormal findings. Serial chest x-rays showed progressive decrease in size of the pulmonary infiltrate, which became miliary in type and sharper in delineation and affected chiefly the midlung fields, with clearing of the abnormality at the right costophrenic angle (figure 2). At the same time the white cells increased progressively to a count of 32,000, with 22% neutrophils and 55% eosinophils on the seventh

hospital day. On the eighth hospital day prednisone was given in a divided dose of 80 mg. daily, and on the following day the white cell count was 14,400, with 74% neutrophils and 1% eosinophils. Symptoms improved rapidly. On the twelfth hospital day a chest film was entirely normal and the patient was free of chest symptoms. He was discharged on a gradually decreasing dose of prednisone and continued free of symptoms. One week after discharge and one day after cessation of prednisone a chest x-ray was negative (figure 3), and the white cell count was 11,200, with 52% neutrophils and 1% eosinophils. Subsequently, over a period of 18 months, he has remained clinically well, with continued normal chest x-rays and blood counts.

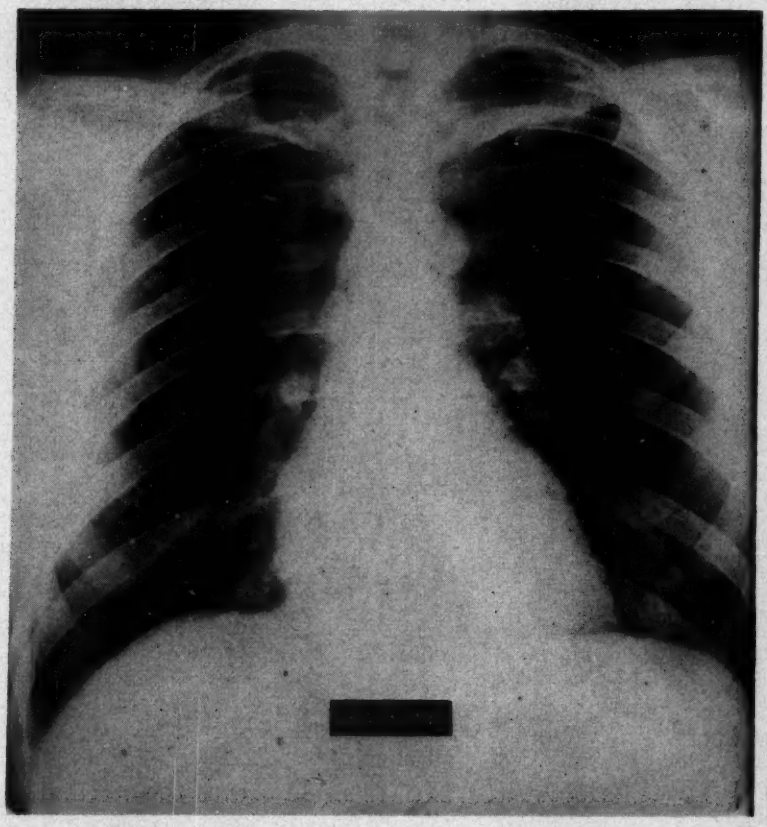

FIG. 3. Chest x-ray taken seven weeks after smoke exposure and following treatment with prednisone shows complete clearing of pulmonary infiltration.

COMMENT

Pulmonary infiltration with eosinophilia has been attributed to infestation with various intestinal parasites. It has occurred during the course of occasional bacterial or protozoal infections, and has developed following the administration of sulfonamides and penicillin in oil and beeswax. It has often appeared in the context of other allergic manifestations, and in many instances the cause has been unknown. Although most of the known or suspected causative agents

have not been inhalants, several cases have been attributed to agents introduced via the pulmonary airways. Pollens of the privet plant and lily-of-the-valley have been implicated.[4, 5] Coccidioidal infection has presented in this fashion.[1, 6] Experimentally, Löffler's syndrome has been duplicated in part by intratracheal instillation of horse serum in sensitized animals.[7]

It has been suggested that this syndrome represents the most benign and reversible expression of pulmonary allergic responses to a variety of antigenic stimuli. This allergic reaction may produce a clinical picture of simple transitory pulmonary infiltration with eosinophilia of variable duration, with or without other atopic manifestations. More profound reactions may show pulmonary vascular phenomena, such as hypersensitivity angiitis,[8, 9] allergic granulomatous angiitis [10] or periarteritis nodosa, with or without widespread visceral lesions.[1, 8, 11, 12, 13]

The present case presents the features originally described by Löffler,[14] namely, (1) transient pulmonary infiltrates, (2) peripheral blood eosinophilia, (3) relative absence of symptoms or physical findings in the chest, and (4) a benign clinical course. It should be noted that the immediate chest symptoms due to the direct irritant effect of the noxious fumes subsided after a few hours, and chest symptoms were subsequently absent for a period of two weeks. This latent period before the development of progressive symptoms and pulmonary infiltrations was further documented by the negative chest microfilm obtained two weeks after the exposure. The pulmonary inflammatory process which subsequently developed was apparently interstitial in location, as evidenced by the absence of râles, wheezes or signs of consolidation on repeated examinations.

It is well known that the inhalation of noxious fumes may produce an immediate pulmonary inflammatory reaction by direct irritant effect of the gases. Among the more dangerous primary irritants present in smoke fumes are aldehydes and acid anhydrides.[15] Two other noxious gases are particularly important, since they both occur under circumstances of combustion and may produce a severe and delayed pulmonary injury. Nitrogen dioxide ("nitrous fumes") may result from combustion of many organic substances containing the nitrous radical. Phosgene gas may be formed as a thermal decomposition product of carbon tetrachloride and other chemicals used in fighting fires. Both of these gases produce an acute but usually delayed bronchitis and bronchiolitis, which may progress to the picture of bronchiolitis fibrosa obliterans.[16, 17] Exposure to nitrogen dioxide fumes from silage gas has recently been reported to produce a pulmonary picture similar to that in the present case.[18, 19, 20] Those cases which have come to autopsy have shown findings of bronchiolitis obliterans. However, in the reported cases of "silo-filler's disease," symptoms did not relent completely during the two- to three-week period of relative remission after exposure. The onset of the second phase, with progression of symptoms, is accompanied by chills, fever, dyspnea, cyanosis and the presence of numerous fine moist râles and expiratory wheezes characteristic of bronchiolar inflammation. Peripheral blood eosinophilia has not been reported in these cases. In the present case the complete absence of respiratory symptoms for two weeks after exposure, along with the normal chest x-ray soon thereafter, the absence of physical findings in the chest throughout the entire course, and the marked eosinophilia, is in distinct contrast to the characteristics of nitrogen dioxide exposure. Also, careful investigation disclosed no likely source of nitrogen dioxide or phosgene gas. No

unusual materials or chemicals were present in the burning building other than large quantities of synthetic fabric consisting of saponified cellulose acetate, which would not produce nitrogen dioxide on combustion. The possibility that the inciting agent evolved from the dyes used in the fabric cannot be ruled out. Chromium, nickel and possibly other metals are known to be potent sensitizers. The possibility that volatile compounds arose upon heating such metals to extreme temperatures likewise cannot be excluded, since some metallic plated articles were present in the store.

An infectious etiology in the present case seems most unlikely, in view of the absence of fever or other signs of infection and the negative diagnostic tests for several possible etiologic agents.

A distinct latent period was noted before the onset of manifestations of an interstitial inflammatory reaction with subsequent eosinophilia. This seems consistent with the hypothesis of a delayed type of allergic inflammatory response to an unknown antigen introduced at the time of the initial smoke inhalation. The development of sensitization thus required some two weeks, a time interval consistent with that necessary for the formation of antibodies to known antigens. It has been adequately demonstrated that certain simple chemical compounds may act as antigens after conjugation in vivo with tissue protein, sensitivity becoming manifest after a latent period of from five to 20 days.[21] This simple chemical allergenic effect apparently differs from the atopic syndromes in that the capacity to become so sensitized is a normal function possessed to a variable degree by all animals. In this instance the lung acts as the specific sensitized tissue or "shock organ," and the antigen-antibody reaction produces an inflammatory response predominantly involving small vessels and capillaries within the pulmonary interstitial tissues. In addition, use of a primary irritant concentration of a sensitizer greatly increases the probability of subsequent sensitization.[21] In this case the initial chemical irritant effect of the inhaled noxious gases may have contributed to the allergenic effect.

The marked and prompt response to prednisone in this and other examples of Löffler's syndrome does not necessarily confirm the immunologic hypothesis, since recent evidence suggests that the action of adrenal corticosteroids on hypersensitivity phenomena may not be due to suppression of antibody formation or antigen-antibody union, but to their capacity to act directly at the tissue level on small blood vessels and capillaries, altering their response to certain irritants, regardless of any immune mechanism in the inflammatory process.[22] Nevertheless, rapid suppression of the inflammatory reaction and protection of the mesenchymal tissues from the effects of antigen-antibody interaction are of extreme importance at this stage if future irreversible complications, such as interstitial fibrosis or necrotizing angiitis, are to be prevented.

Summary

1. A case of transitory pulmonary infiltration and eosinophilia (Löffler's syndrome) following smoke inhalation is reported.

2. The clinical course presented certain features suggesting as the pathogenesis for this syndrome a delayed type of allergic response in the lungs to an unknown antigen in the smoke.

3. A dramatic and complete resolution followed the administration of prednisone.

Summario in Interlingua

Un pumpero disveloppava grados crescente de tensitate thoracic, de dyspnea, e de tusse duo septimanas post le inhalation de fumo. In despecto del crescente severitate del symptomas, le patiente remaneva sin febre e libere de signos physic durante le complete curso de su maladia. Un roentgenogramma initial, obtenite al tempore del declaration del symptomas, esseva negative, sed un secunde roentgenogramma, obtenite quatro septimanas post le exposition al fumo e duo septimanas post le declaration del symptomas, revelava extense maculas de infiltration pulmonar que deveniva, subsequentemente, de plus in plus nodular e miliari. Le numeration leucocytic total montava a 32.000, con 55% de eosinophilos. Altere examines laboratorial—incluse le urinanalyse, determinationes del proteinas seral e de cryo-agglutininas, e tests pro specific agentes infectiose—esseva negative. Un historia personal o familial de atopia non poteva esser establite. Le exposition a gases nocive—per exemplo a dioxydo de nitrogeno o a phosgeno—esseva excludite, sed il remaneva le possibilitate de sensibilisation a vapores metallic ab chromo, nickel, o altere elementos.

Le distincte periodo de latentia, precedente in iste caso le disveloppamento de symptomas e de signos roentgenographic, es compatibile con le hypothese que il se tractava hic de un typo tardive de allergic responsa inflammatori a un non cognoscite allergeno que esseva introducite per le inhalation de fumo. Isto significarea que le pulmon ageva como le specific histo sensibilisate, e le reaction de antigeno e anticorpore produceva un responsa allergic que interessava le histos mesenchymal intra le parenchyma pulmonar.

Un marcate e rapide subsidentia del symptomas e le permanente clarification del anormalitates roentgenographic sequeva le administration de prednisona. Es formulate le opinion que le prompte e rapide suppression del allergic reactiones inflammatori intra le histos mesenchymal es del plus grande importantia si le complicationes possibile de fibrosis interstitial o de angiitis necrotisante debe esser prevenite.

Le presente caso supporta le conception que—in despecto de multiple causas—le pathogenese fundamental in infiltration eosinophilic del pulmon es probabilemente un question de reactiones de hypersensibilitate a varie agents antigenic al quales le histos pulmonar esseva exponite.

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LIVER ABSCESS DUE TO *CLOSTRIDIUM PERFRINGENS* *

By RAYMOND M. KIVEL, *San Francisco, California,* ALEXANDER KESSLER, *Bronx, New York,* and DONALD J. CAMERON, *New York, N. Y.*

INTRODUCTION

ALTHOUGH clostridia are widely distributed in nature and are normal inhabitants of the human intestine, their invasiveness as pathogens is usually related to some sort of physical trauma with local tissue destruction. Clostridia, however, may often be present at the site of accidental or surgical trauma without causing clinical infection. This close association of clostridial infection with trauma, together with the rarity of other clinical types of infection, has been considered as evidence that some peculiar host factors, usually presumed to be necrotic tissue without oxygen supply, are required for initiation of infection by these organisms.

The present report is that of a patient with an illness of obscure origin who proved to have a hepatic abscess due to *Clostridium perfringens*. The unusual

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nature of this infection, its association with bacteremia and pneumoperitoneum in the absence of intestinal perforation, together with clinical and postmortem observations, will be reviewed. Some of the peculiarities of clostridial infections will be discussed.

Case Report

A 68 year old white woman was admitted to a general medical ward of Bellevue Hospital on October 5, 1955, because of weakness, anorexia and nausea of four days' duration. Fourteen years previously she had been found to have diabetes. She had been taking 20 to 40 units of protamine zinc insulin daily, but had omitted this during her present illness. On the day before admission she had experienced some lower abdominal cramps. She denied diarrhea, vomiting, fever, chills and intolerance to fatty food. Additional history and review of systems were noncontributory.

Physical examination revealed an obese elderly woman who appeared acutely ill. The pulse rate was 100 per minute; blood pressure, 160/80 mm. Hg; respirations, 30 per minute, temperature, 102° F. The heart and lungs were normal. There was inconstant tenderness on deep palpation in the suprapubic and epigastric areas. No masses could be felt, and the bowel sounds were normal. The patient vomited during the examination.

On admission the leukocyte count was 22,000 per cubic millimeter, with 44% adult neutrophils, 46% band forms, 8% lymphocytes, 1% monocytes and 1% eosinophils. The hemoglobin was 12 gm. per 100 c.c., and the hematocrit was 35%. The erythrocyte sedimentation rate was 38 mm. per hour (Wintrobe). Urinalysis showed a pH of 5.0, 1 plus albumin, 4 plus sugar and 4 plus acetone. The urine sediment contained innumerable leukocytes, many of which were clumped. The vomitus and stool contained no occult blood by guaiac test. The blood chemical examination revealed the following: sugar, 364 mg. per 100 c.c.; sodium, 120 mEq./L.; carbon dioxide, 19.1 mEq./L.; chloride, 108 mEq./L.; urea nitrogen, 57 mg. per 100 c.c.

The patient was treated with insulin and saline infusions, and the glycosuria and acetonuria cleared within four hours. Her diabetes remained well controlled during the rest of her hospitalization. Urine cultures and blood cultures were obtained on admission. Because of the pyuria, intramuscular tetracycline was started. Two hours after admission the cardiac rhythm was noted to be irregular, and an electrocardiogram confirmed the presence of auricular fibrillation. During the next few hours she received ouabain intravenously, and the electrocardiogram indicated a return to normal sinus rhythm. Thereafter she was treated with digitoxin.

The patient soon began to appear more gravely ill, with temperature rising to 103° F. and with rapid, shallow respirations. Later that day she vomited about 1,000 c.c. of greenish and then coffee-ground material which contained blood by guaiac test. Wangensteen suction was started. At this time the hematocrit was 30% and the leukocyte count 10,000 per cubic millimeter. The reticulocyte count was 0.4%. The serum appeared slightly icteric.

On the second day there was little change clinically. The abdominal tenderness in the right upper quadrant was more marked. The skin seemed slightly icteric, and the breath had a peculiar, unidentifiable odor. Additional blood chemical examinations revealed: icterus index, 33 units; cephalin flocculation, 0; alkaline phosphatase, 5.5 Bodansky units; total protein, 6.2 gm. per 100 c.c., with albumin, 3.6, and globulin, 2.6; cholesterol, 264 mg. per 100 c.c., with 23 mg. per 100 c.c. esters; amylase, 66 units; prothrombin time, 19.8 seconds (control, 15.7). The urine contained 1 plus bile by the Harrison spot test, and urobilinogen in a 1:16 dilution.

On the third day the patient was delirious and had a continuously elevated temperature. The right upper quadrant of the abdomen was guarded and the bowel

sounds were distant. A blood transfusion was given and intramuscular streptomycin started.

On the morning of the fourth day the patient appeared to be improved. The temperature was 100.4° F., and she was able to take some fluids by mouth. By evening, however, she was comatose and her temperature again was 103° F. Hand movements suggestive of "liver flap" were observed. The respiratory rate had risen to 60 per minute. The impression of impending hepatic coma prompted administration of 40 gm. of sodium glutamate, 200 mg. of hydrocortisone, and a mixture of 5% carbon dioxide and 95% oxygen by mask. Little change was noted during this and the following day. Additional blood chemical examinations revealed: urea nitrogen, 59 mg. per 100 c.c.; icterus index, 5 units; cephalin flocculation, 0. The blood pH was 7.4; carbon dioxide, 25.5 mEq./L.; sodium, 138 mEq./L.; chloride, 112 mEq./L. The blood ammonia level was 1.5 μg. per cubic centimeter (normal, 0.5 to 1.0 μg. per cubic centimeter).

A survey roentgenogram of the abdomen demonstrated a central large round bubble, interpreted as dilated stomach. The patient was fluoroscoped in the sitting position, and under the right leaf of the diaphragm there was a well demarcated area of radiolucency confirmed by roentgenogram. This finding was thought to be characteristic of free air within the peritoneal cavity, and was attributed to perforation of a hollow viscus. The patient was therefore taken to the operating room, and under general anesthesia a right rectus incision was made. There was evidence of generalized peritonitis, with cloudy peritoneal fluid, most marked in the right upper quadrant and the right colic gutter. The stomach and the hepatic flexure of the colon were adherent to the inferior surface of the right lobe of the liver. An abscess measuring about 10 cm. in diameter was present in the left lobe of the liver. The abscess was debrided. No perforation of a hollow viscus could be found. The appendix appeared to be normal. Stones were felt in the common bile duct. Because of the patient's precarious condition no other examination or procedure was carried out. Postoperatively her blood pressure gradually fell despite blood transfusions and Levophed infusion, and she died the next morning.

Both of the blood cultures taken on admission yielded growth of a large anaerobic gram-positive bacillus which had the cultural characteristics of *Clostridium perfringens*. The same organism was isolated from the gall-bladder bile taken at operation. A gram stain of material from the liver abscess revealed similar gram-positive bacilli, and *C. perfringens* was isolated from the pus taken from this abscess.

Autopsy Report: Postmortem examination was performed within six hours of death. Both pleural cavities contained small amounts of straw-colored fluid. The abdominal cavity contained a large amount of clotted blood. On the peritoneal surface of the right diaphragm there was a bright green fibrinous exudate. The liver weighed 1,800 gm., was tan and soft, and felt slightly greasy. In the left lobe there was a large cavity which opened on the lower edge of the liver. The cavity wall was shaggy and appeared to consist of hemorrhagic, necrotic, hepatic parenchyma. Adjoining it were several small dark red areas, 2 to 5 mm. in diameter, suggestive of cavities filled with blood. A thrombus was present in a branch of the portal vein near the abscess. The hepatic ducts were slightly dilated.

Microscopic examination revealed that the abscess cavity contained necrotic material, inflammatory cells, and colonies of bacilli. The wall proper was composed of loose inflammatory tissue and of compressed hepatic cells, many of which had undergone coagulation necrosis (figure 1). There were many small cavities filled with blood and large bubbles of gas lined by colonies of bacilli. Other than a moderate amount of fatty change, the remainder of the liver was unremarkable.

The gall-bladder was greatly dilated and contained green bile but no calculi. The common bile duct was dilated to about 4 cm. in circumference. Calculi were

present throughout its entire length, and extended up into the hepatic ducts and their smaller branches. They appeared yellow, and varied in size from sandlike to stones 1 cm. in diameter. When the ducts were traced no evidence of acute inflammation was found. No evidence of infection by clostridia was found in any other tissue, nor were there other significant pathologic findings. The final pathologic diagnosis was liver abscess due to *C. perfringens.*

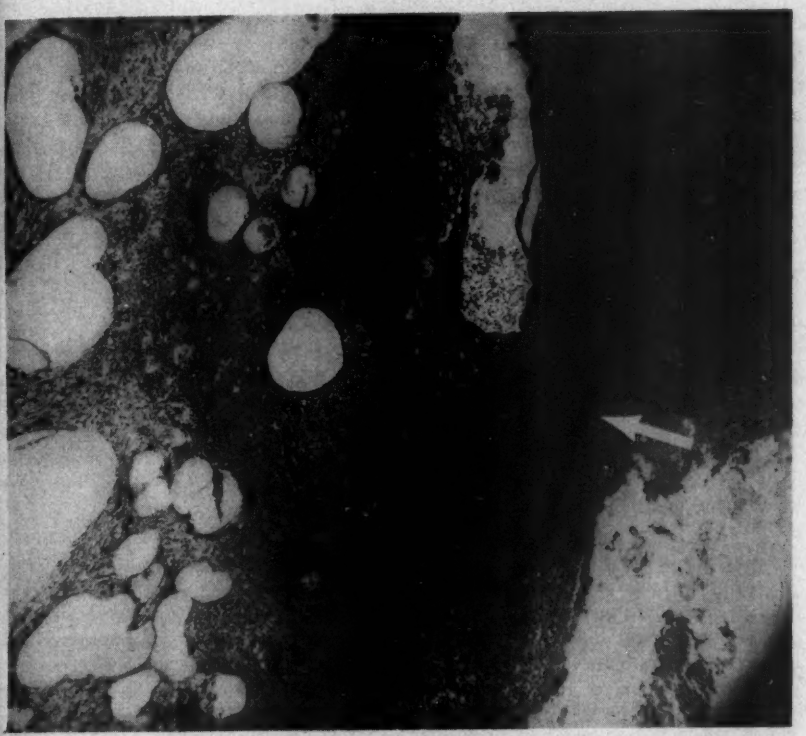

FIG. 1. Photomicrograph of a section of the liver abscess. The left half of the field shows the abscess wall with gas bubbles and compressed liver parenchyma. The right half includes contents of the abscess cavity with necrotic material. The arrow points to masses of gram-positive bacilli.

COMMENT

As has been noted, members of the Clostridium group of microörganisms are quite selective in the organs they infect. Trauma of muscle, especially when the wound is deep and dirty, predisposes to gas gangrene, by far the most common of clostridial infections. This dread complication of wounds is an acutely spreading gangrene, characterized by the production of large amounts of gas in the tissues at the site of infection and by toxemia due to the exotoxin. A collective review[1] of over 3,000 wounds showed contamination by clostridia in 14.7%, whereas an average of only 1.76% of 187,936 wounds were classed as being *infected* with clostridia.

Clostridia may be introduced into the uterus from the vaginal canal in induced (usually criminal) abortions. In the more severe cases septicemia occurs, usually resulting in shock and death. Gas peritonitis may follow perforation of an abdominal viscus or laparotomy. In the latter instance, gas gangrene of the abdominal wall may develop. "Spontaneous" gas peritonitis, i.e., without intestinal perforation, has been reported.[2] Welch [3] believed that some cases of pneumaturia were caused by clostridial infections of the genitourinary tract. Madison [4] found no accounts of perinephric abscess due to *C. perfringens* prior to the patient he reported. Large septic lung infarcts or the aspiration of infected material may give rise to gangrene of the lung caused by clostridia.[5] *C. perfringens* bacterial endocarditis has been documented at autopsy.[6]

Cultures of the stomach and duodenum rarely show clostridia, and infections arising from the upper alimentary tract are infrequent.[7] Nevertheless, the presence of this microörganism in the diseased biliary tract is relatively common.[8] Gordon-Taylor and Whitby,[9] in summarizing the literature on the bacteriology of the diseased gall-bladder, found that *C. perfringens* could be obtained from the bile in an average of 0.31% of all cases (both infected and uninfected), from the gall-bladder wall in 2.6% and from calculi in 4.2%. In infected cases the yield was higher, namely, 0.79%, 3.9% and 12.7%, respectively. As evidence of the variability of bacterial studies of the gall-bladder, *C. perfringens* has been recovered from the gall-bladder wall in as high as 22% of cultures.[10]

When one considers the frequency with which clostridia are found in the biliary tract, it is puzzling that the liver is not more often infected. While the biliary tree is a well recognized source of pyogenic liver abscess, most reviews of that subject [11] do not mention clostridia as an etiologic agent.

Welch, in his classic paper on "Morbid Conditions Caused by *Bacillus aerogenes capsulatus*," [3] cited reports of multiple hepatic abscesses caused by *C. perfringens,* and remarked: "From the foregoing cases it is to be inferred that the gas bacillus may invade the bile ducts and gall bladder from the intestine sometimes during life, and that it may not only produce gas but necrosis and purulent inflammation. The presence of gall stones, cancer of the bile ducts and operations on the gall bladder favor this mode of infection." In 1900 Pratt and Fulton [12] reported multiple small liver abscesses, found especially about the intrahepatic bile ducts, in a patient who died after a cholecystostomy for obstructive carcinoma of the common bile duct. In a discussion of abscess of the liver, Beaver [13] stated that occasionally members of the genus Clostridium, including *C. perfringens,* are the responsible pathogens. Flynn's review of the literature on pyogenic liver abscess [14] mentions *C. perfringens* among the "organisms that are rarely found."

In our patient the isolation of *C. perfringens* from the blood, from the bile, from the liver abscess itself and from the peritoneal exudate, as well as the presence of large amounts of intraperitoneal gas in the absence of perforation of a hollow viscus, indicated that this organism played a dominant, if not exclusive, role in her illness and death. That the abscess wall on microscopic examination contained gas bubbles and many clumps of large gram-positive bacilli (presumably *C. perfringens*), and was relatively devoid of the purulent exudate usually associated with pyogenic abscess, suggests that Clostridium was the chief and perhaps the sole pathogenic microörganism.

Clinically, the extremely toxic appearance of the patient and the delirium seemed out of keeping with the usual reaction to this degree of fever and infection. Another feature of considerable interest was the peculiar odor of the patient's breath. It was identical with the odor noted after stormy fermentation of culture media, and was thought to be due to butyric acid, a product of *C. perfringens* action on carbohydrates. In other respects the clinical findings were similar to those in either cholangitis or hepatic abscess secondary to other pyogenic microörganisms.

The reasons for the paucity of *C. perfringens* hepatic infections and the factors involved in establishing an abscess, particularly a solitary abscess such as in the present case report, are not clear. Some studies with dogs as well as with material from humans [15] would suggest that clostridia are common inhabitants of the liver. Nevertheless, although dogs are known frequently to harbor clostridia in their livers, the studies of Sborov et al.[16] convincingly demonstrate that this is not the case with living humans. In this study, anaerobic cultures were made of material obtained in 86 needle biopsies of the liver in 66 patients. In no instance was Clostridium recovered. Welch's statement [3] that the gas bacillus invades the bile ducts from the intestine and then travels to the liver seems supported by the few case reports on the subject. In the present case the mode of entry may well have been in this manner.

Little is known about the host factors that favor the development of clostridial infection. Shock, malnutrition, anemia, arteriosclerosis and diabetes are often said to enhance the development of gas gangrene. Diabetics are particularly prone to develop gas gangrene following amputation, even through an apparently "clean field." [17] The experiments of Chau et al.,[18] involving hepatic artery ligation in dogs, suggest that lowered oxygen tension may play a role in enhancing virulence of clostridia. Within several hours of ligation of the artery, needle biopsies of the liver yielded *C. perfringens*, and at necropsy the liver showed varying degrees of necrosis, with large numbers of typical gram-positive bacilli as well as gas bubbles in the portal veins and sinusoids.

In a setting of cholestasis, intrahepatic portal vein thrombosis, dehydration and acidosis, it may be postulated that liver circulation—and thereby oxygenation—were impaired in the patient herein reported, allowing a favorable milieu for the growth of anaerobic organisms. In addition, the presence of diabetes may in some way have made the liver a more suitable culture medium.

Summary

A case report is presented of a patient who had a solitary liver abscess due to *C. perfringens*. The most noteworthy clinical feature in this case was the presence of *C. perfringens* bacteremia and of pneumoperitoneum in the absence of perforation of a hollow viscus. The operative findings are presented and the postmortem examination is detailed. A brief survey of the literature is given, with emphasis on the various organs known to be infected by clostridia, and the rarity of liver involvement is noted. Reduced oxygen tension in the liver and hyperglycemia in this patient are considered as possible factors which permitted invasion of the liver by clostridia from the gut by way of the biliary tract.

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SUMMARIO IN INTERLINGUA

Es presentate le caso de un patiente qui habeva un abscesso hepatic solitari, causate per *Clostridium perfringens*. Le plus notabile aspecto del caso esseva le presentia de bacteremia a *Cl. perfringens* e pneumoperitoneo in le absentia de perforation de un viscere cave.

Le patiente, un femina diabetic de 68 annos de etate, esseva acutemente malade al tempore de su admission al hospital. Illa esseva febril e levemente icteric. Su abdomine superior esseva levemente sensibile sub pression. Le roentgenogramma del abdomine revelava un collection de gas infra le diaphragma. Post iste constatation, exploration chirurgic del abdomine esseva interprendite, e un grande abscesso esseva trovate in le lobo sinistre del hepate. Le patiente moriva le die post le operation. Culturas de sanguine e etiam culturas de bile e del abscesso hepatic produceva *Cl. perfringens*.

Le necropsia revelava—a parte le abscesso del hepate—un thrombo in un tributario del vena portal proxime al sito del abscesso. Le abscesso proprie consisteva de necrotic cellulas hepatic, cellulas inflammatori, e multe colonias de grande bacillos. Le pariete del abscesso contineva numerose cavitates, plenate de gas e revestite de colonias de bacillos. Numerose calculos esseva presente in le ducto biliari commun e etiam in le ductos hepatic.

Es presentate un breve revista del litteratura concernite con infectiones per clostridios. Es opinate que in le caso del presente reporto, cholestase, thrombose intrahepatic del vena portal, dishydratation, e acidose obstrueva possibilemente le circulation hepatic e provideva un milieu favorabile pro le crescentia del anaerobie micro-organismos mentionate.

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RECURRENT FOCAL GLOMERULITIS: A CASE REPORT WITH RENAL BIOPSY *

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Focal glomerulitis has been a recognized clinical entity since 1914, when it was described by Volhard and Fahr.[1] However, the clinical history and urinary findings may be indistinguishable from acute glomerulonephritis, with which it is often confused.[2] This presentation includes a case with the classic clinical, laboratory and pathologic findings of focal glomerulitis, which was diagnosed on four separate occasions in different institutions as glomerulonephritis. This is the first case to the authors' knowledge which has been studied by renal biopsy.

Case Report

A 28 year old white male farmer was admitted to the hospital on June 2, 1956, with complaints of sore throat and headache of one week's duration. Four days after the onset of the sore throat he developed backache, chills, fever, nausea and dark urine. He had received penicillin on three successive days prior to admission. At the time of admission the fever and backache had subsided, but the urine was still dark brown.

The patient had suffered at least three similar episodes in the preceding six years. The first attack, in the winter of 1949–50, had consisted of a sore throat, followed in a day or two by back pain and dark red urine. There was no edema. He was treated at home by his family physician with a six-to-eight-day course of penicillin, and had completely recovered within two weeks. He felt well until May, 1951, when he began to complain of malaise and lassitude. After four days he developed signs of an upper respiratory tract infection, which progressed to acute laryngitis and tonsillitis. On May 11 he visited his physician and received an injection of penicillin. On May 15, he began to pass bright red urine, and noted backache, chills, fever and headache. He had no swelling of the hands, feet or face. He was admitted to a Veterans Administration Hospital on May 18, 1951. The temperature was normal, the pulse rate 70 per minute. The blood pressure was 130/80 mm. of Hg. He was

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found to have follicular tonsillitis, a grade II apical systolic murmur, and a palpable liver and spleen. No edema was present. Initial urinalysis revealed many red cells, a few white cells and a trace of albumin. Specific gravity was 1.016. Repeated urine examinations thereafter showed occasional red and white cells, no casts or albumin, and specific gravity ranging from 1.002 to 1.015. The patient was treated with penicillin. He refused to accept a program of prolonged bed-rest, and was discharged after seven days of hospitalization with diagnoses of tonsillitis and chronic glomerulonephritis. He felt completely well and returned to his usual job.

Approximately two weeks following his discharge the patient had a recurrence of sore throat, accompanied by back pain and dark brown urine. At this time he also complained of an abscessed tooth. He applied for admission to a Veterans Administration Hospital, but during the two-week delay before his admission the symptoms subsided. Physical examination on admission revealed a normal temperature and pulse. The blood pressure was 112/58 mm. of Hg. The tonsils were small and the throat was mildly injected. The heart and lungs were normal. The spleen was palpable and the liver questionably felt one fingerbreadth below the costal margin. There were a few shotty nodes in each axilla. The remainder of the examination was considered to be normal. The urine on three separate examinations was negative for cells, casts and albumin. Specific gravity varied from 1.015 to 1.020. Intravenous pyelograms were normal, as was the blood nonprotein nitrogen. Examination for urinary porphyrins was negative. The sedimentation rate was 2 mm. The patient was discharged feeling well, and had no further difficulty until the present illness.

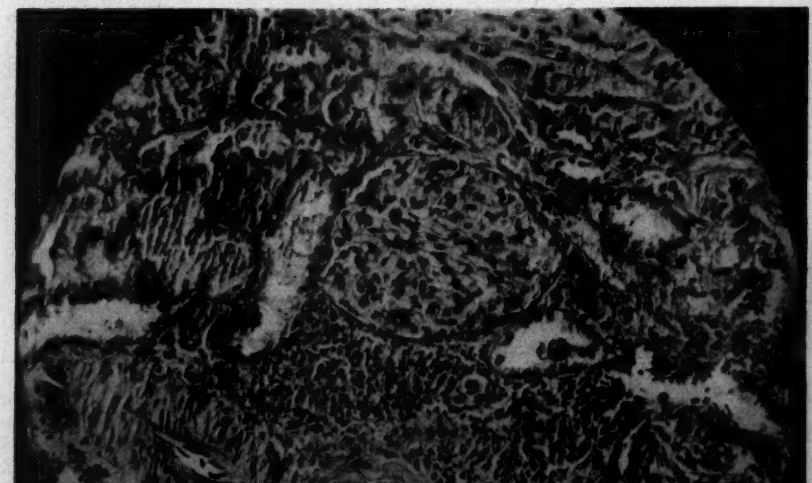

FIG. 1. Photomicrograph showing a normal glomerulus and a focal collection of inflammatory cells.

Physical examination on the present admission showed a temperature of 98.4° F.; blood pressure, 130/70 mm. of Hg; pulse rate, 80 per minute. There was no edema of the face or extremities. A subsiding follicular tonsillitis was present. There was a grade II apical systolic murmur. The liver and spleen were not palpable. The remainder of the examination was normal. Urinalysis revealed 3 plus albuminuria, numerous red blood cells, occasional white cells, and many hyaline, granular and red cell casts. Throat culture grew beta hemolytic streptococci; urine culture showed no growth. The blood urea nitrogen was normal. The patient was treated with penicillin, with prompt recovery. Two weeks after admission the urine was free of cells, casts and albumin. Phenolsulfonphthalein test showed 25% excretion in the first 15 minutes and 60% excretion in two hours. He was able to concentrate the urine to a specific gravity of 1.030 to 1.035. Renal biopsy performed on June 29 was reported by Dr. Beulah Hathaway as follows: "The section shows a small accumulation of lymphocytes and monocytes about one blood vessel and partial fibrosis of a single glomerulus. One other glomerulus shows one or two polymorphonuclear cells. Other glomeruli and tubules show no significant change. No evidence of a diffuse renal disease such as acute or chronic glomerulonephritis is present" (figure 1).

Discussion

In summary, this patient had four attacks of tonsillitis or pharyngitis, followed in two to four days by back pain and hematuria. Edema and hypertension were consistently absent, and apparent complete recovery was rapid.

Differentiation between focal glomerulitis and acute or chronic glomerulonephritis is important from both the prognostic and the therapeutic standpoint. Focal glomerulitis is a benign, self-limited disease requiring no specific treatment except of the accompanying infection, whereas acute glomerulonephritis is usually considered to be an indication for prolonged bed-rest. The development of albumin, red blood cells and, in particular, red cell casts in the urine following a streptococcal infection is ordinarily regarded as prima-facie evidence of glomerulonephritis. Yet in this case such a diagnosis was in doubt on clinical grounds and was not substantiated by renal biopsy. If the illness is regarded as one of glomerulonephritis, the separate attacks may be considered as either recurrent acute glomerulonephritis or acute exacerbations of chronic glomerulonephritis. In the first instance it would be difficult to explain the absence of longer latent periods between the respiratory and renal manifestations.[3] Furthermore, the chances of four independent attacks of acute glomerulonephritis in the same individual would be extremely unlikely.[4] In the second instance it would be difficult to account for the absence of edema, hypertension and residual urinary changes between attacks, and for the rapid recovery without sequelae. The essential differential points are illustrated in table 1.

It is well recognized that microscopic hematuria is commonly seen during or immediately following acute infections, especially in childhood.[5, 6, 7] This may well represent subclinical focal glomerulitis. It is our belief that this entity is frequently and perhaps even usually confused with acute glomerulonephritis. Some authors,[2] in fact, hold that the two diseases cannot be clinically separated. In case of doubt, a renal biopsy seems well worth while, since the prognostic implications of the two conditions are vastly different.

The exact nature of the renal lesion in focal glomerulitis has not been established. Some authors [7] have proposed that actual bacterial invasion of the blood

TABLE 1

	Focal Glomerulitis	Acute Glomerulonephritis	Acute Exacerbation of Chronic Glomerulonephritis
Latent period	Height of infection	One to four weeks	Two to four days
Edema	Absent	Usually present	Frequent
Hypertension	Absent	Usually transiently present	Usual
Duration of urinary abnormalities	One to two weeks	One to six months	Persistent
Recurrences	Common	Extremely rare	May occur
Sequelae	Complete healing	(1) Healing with or without defect (2) Progression to subacute or chronic	Eventual progression
Nitrogen retention	Very rare	May occur	Usual
Biopsy	Focal changes	Diffuse changes	Diffuse changes

occurs, and state that the organism can be recovered from the blood and the kidney at necropsy. Others favor an allergenic mechanism, and believe that such a response might well be focal rather than generalized.[8] The concept of local tissue allergy has recently been emphasized by the production of skin sensitivity to streptococcal toxins in patients previously affected with erysipelas.[9] We believe the same mechanism, with the kidney as the sensitized organ, may well be the explanation for the recurrent episodes of focal glomerulitis. If this is true, actual bacterial invasion of the kidney may not be necessary to produce the urinary changes of focal glomerulitis. In general, there is lack of unanimity of opinion as to etiology, pathology and clinical picture of this entity.[10] From the standpoint of cultures, it was unfortunate that this patient had received penicillin therapy prior to admission. Furthermore, the biopsy was done when the renal lesion was almost healed.

The diagnosis of glomerulonephritis has in the past often been made on the basis of history and urinary findings. With the advent of technics for renal biopsy it has become apparent that many pathologic conditions can mimic the clinical and urinary picture.[11] It is our belief that many cases of "glomerulonephritis" may well be focal glomerulitis. It is hoped that renal biopsy technics will further clarify this entity.

SUMMARY

A case believed to represent focal glomerulitis has been presented. Since this case demonstrated many of the findings usually seen in glomerulonephritis, the differentiating features of the two illnesses are discussed. The present case was substantiated by renal biopsy.

Summario in Interlingua

Glomerulitis focal es un recognoscite entitate clinic depost 1914. Nonobstante, le reporto de un caso con le classic characteristicas clinic, laboratorial, e pathologic es hic presentate a causa del facto que le historia clinic e le constatationes urinari in glomerulitis focal es a vices difficilissime a distinguer ab illos de glomerulonephritis acute.

Le patiente, un fermero de racia blanc de 28 annos de etate, esseva hospitalisate con le gravamines de mal de gurgite e mal de capite de un duration de un septimana e de dorsalgia, nausea, e urina obscur de un duration de tres dies. In le curso del passate sex annos ille habeva habite al minus tres episodios del mesme genere.

Le examine physic monstrava solmente tonsillitis follicular in un stadio de subsidentia. Esseva notate nulle edema e nulle elevation del pression de sanguine. Le urinanalyse monstrava albuminuria del grado 3 plus, numerose erythrocytos, sporadic leucocytos, e multe cylindros hyalin, granular, e erythrocytic. Le nitrogeno del urea sanguinee esseva normal. Le urina esseva sterile. Streptococcos hemolytic beta esseva obtenite in culturas ab le gurgite. Le patiente esseva tractate con penicillina. Le resultato esseva un prompte restablimento, e duo septimanas plus tarde le tests de function renal e le urinanalyse esseva completemente normal. Le biopsia renal monstrava un micre collection de chronic cellulas inflammatori circum un vaso de sanguine, sin ulle evidentia de glomerulonephritis acute o chronic.

Glomerulitis focal pote esser distinguite ab glomerulonephritis acute per le apparition del anormalitates urinari al culmine del infection (plus tosto que post un periodo latente) e per le absentia de edema, hypertension, e retention de nitrogeno. Illo pote esser distinguite ab exacerbationes de glomerulonephritis chronic per le prompte retorno de tests del urina e del function renal al stato normal.

Le natura del pathogenese non es exactemente establite, sed il es probabile que il se tracta de un ver invasion bacterial del renes o de un local reaction allergic al presentia de streptococcos, con le renes representante le previemente sensibilisate organo.

Es exprimite le opinion que multe casos identificate como "glomerulonephritis" es probabilemente de facto glomerulitis focal. Proque le prognose e le therapia differe si vastemente in le duo conditiones, biopsia renal va provar se de valor in casos dubitose.

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ESOPHAGEAL MONILIASIS: REPORT OF A CASE WITH ROENTGENOGRAPHIC FINDINGS*

By S. A. KAUFMAN, M.D., and GEORGE LEVENE, M.D., *Boston, Massachusetts*

INFECTION with *Candida albicans,* a serious side-effect of intensive antibiotic therapy, has been recognized more frequently in recent years. While the more common manifestations of the disease—thrush, vaginitis, dermatitis and bronchopulmonary infections—are well known,[1, 2] the rarer forms have not been too well documented. Esophageal moniliasis is unusual, but presents radiographic findings distinctive enough to suggest the diagnosis in a patient in whom the disease may be unsuspected.

CASE REPORT

A 16 year old white male, admitted to the hospital in January, 1950, had been well until two weeks prior to entry, at which time he first complained of pain in the back, dizziness and weakness. A routine blood examination by his local physician revealed an abnormal blood count, and he was referred to the hospital, where a diagnosis of acute lymphatic leukemia was established. On physical examination generalized lymphadenopathy and splenomegaly were found. His hemoglobin on admission was 10.9 gm.; hematocrit, 31.5%; platelets, 22,640; white blood count, 89,000, with 94% lymphocytes, two blast forms, two metamyelocytes and one myelocyte. The patient had no gastrointestinal symptoms at this time. He received radiation therapy to the spleen and was discharged. He returned two months later to the hospital, having become progressively worse. Several days prior to re-admission he had developed epigastric and substernal pain on swallowing. A gastrointestinal examination showed narrowing and irregularity of the lumen of the entire thoracic esophagus, loss of mucosal markings and absence of peristalsis (figure 1). The gastrointestinal symptoms progressed to a point where the patient was able to take only small sips of fluid. At no time was there evidence of thrush or Monilia infection elsewhere in the body. His treatment in the hospital consisted of blood transfusions, ACTH and other supportive therapy. Following a month of hospitalization the patient died. During the last two weeks of life a rapidly progressive leukopenia was noted.

At postmortem examination the final diagnosis of acute lymphatic leukemia was confirmed. The esophagus showed thickening of the wall, due mostly to a thick coating of yellowish material. This produced a pseudomembrane which lined almost

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the entire lumen. Culture of this remarkable layer grew out *C. albicans*. Microscopic study of the esophagus revealed only a small segment of intact squamous epithelium. The greater part of the specimen showed ulceration and necrosis of the mucosa, which extended through the muscularis in many places. A thick mantle

FIG. 1. Barium swallow. There is marked, irregular narrowing of the thoracic esophagus, with less of the mucosal pattern and absent peristaltic activity.

covered the ulcerated and necrotic portions. This consisted of a solid mass of budding cells, filaments and necrotic debris. Deeper in the submucosa and muscularis were scattered cells with spherical hyperchromatic nuclei and scant cytoplasm. These cells resembled lymphocytes. The adventitial tissue was thickened and contained fibroblastic proliferation and capillarization.

A review of the literature yielded only one communication which described the roentgenographic appearance of esophageal moniliasis. Andrén and Theander [5] reported on two chronically ill patients with oral thrush in whom there was severe infection of the esophagus with *C. albicans*. The roentgenographically demonstrable changes consisted of an irregular, ragged outline of the esophageal lumen. In one case that recovered, the distensibility of the esophagus was lost. In the fatal case the changes had progressed to a marked degree, so that swallowing was impeded. In both patients the cervical esophagus was spared, with the involvement extending throughout the entire thoracic portion. It would appear that the radiographic changes depend on the extent of growth of the organisms. In the present case there was, in addition to the mucosal changes, marked narrowing of the lumen.

The clinical features of the disease include a history of chronic debilitating disease, repeated infection, leukopenia, long treatment with antibiotics and courses of medication with cortisone or ACTH. In cases with oral thrush esophageal involvement should be suspected when there are symptoms of dysphagia. In the patient described at this time there was no evidence of oral thrush, but his complaints of painful swallowing focused attention on his esophagus.

The pathologic findings in esophageal moniliasis consist of ulceration of the mucosa with a growth of *C. albicans* in the esophageal wall. It may be an extension of a severe pharyngeal infection, or it may be localized to the esophagus, and thus the true nature of the disease can be overlooked. It is important, therefore, that any debilitated patient receiving intensive antibiotic therapy who complains of dysphagia or other symptoms of esophageal irritation be examined radiographically. With the application of newer therapeutics for moniliasis,[4] it is important that this condition be recognized.

Summary

The roentgenologic appearance of the esophagus in a patient with leukemia and esophageal moniliasis is presented. Roentgenologic examination because of dysphagia revealed marked irregularity, narrowing and rigidity of the esophagus. This was due to a pseudomembrane produced by an extremely thick growth of *C. albicans*, which lined almost the entire esophageal mucosa.

Summario in Interlingua

Es reportate un caso de moniliasis esophagee in un jevene masculo con leucemia. Infection per *Candida albicans* in le esophago debe esser suspicite in omne patiente qui se plange de dysphagia si ille suffre de un chronic morbo debilitante e ha recipite un prolongate therapia a antibioticos. Il existe, in tal casos, distincte constatationes radiographic que amonta a un restriction irregular del passage esophagee como illo es delineate in le esophagogramma. Isto resulta de un crescentia extense de *C. albicans* in le ulcerate mucosa esophagee. In dependentia del grado de infection, le examine fluoroscopic pote revelar un disturbation del processo inglutitori. Viste le augmentate incidentia de infectiones monilial como effecto lateral de intense therapia a antibioticos, on debe esser preste a recognoscer le presentia de iste plus tosto inusual typo de infection.

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RELAPSING NODULAR NONSUPPURATIVE PANNICULITIS WITH LUNG INVOLVEMENT: CLINICAL AND AUTOPSY FINDINGS, WITH NOTES ON PATHOGENESIS *

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Introduction

Nonsuppurative nodular relapsing febrile panniculitis (Weber-Christian syndrome) is an uncommon clinical entity, and is rare as a cause of death or concurrent with death. Approximately 10 instances have been reported in the literature as autopsied cases.[1, 2, 3, 4] When death has been attributed to fatal systemic panniculitis, the necropsy has revealed widespread involvement of adipose tissue, including the panniculus and mesenteric, omental, retroperitoneal adipose tissue and mucosa of the intestines. Systemic fatal panniculitis has been recently reviewed by Steinberg,[1] and an interesting review of the Weber-Christian syndrome in general has recently been published by Beerman.[6]

This case is reported in view of the interesting nodular pneumonitis found at autopsy and the earlier, surgically removed granulomatous lesion of the jejunum. It is believed that these lesions represent systemic aspects of a singular relapsing febrile disease in a patient manifesting the more classic components of Weber-Christian disease. At the time of autopsy the subcutaneous panniculitis was seen in one area and showed the earliest minimal changes.[7] It is also felt that this case provides interesting data for postulations and possible future studies of the nature of Weber-Christian syndrome.

Case Report

A. Clinical Findings:

1. *First Admission:* Present Illness: A 64 year old white male clerk in the Marine Corps was admitted to the Veterans Administration Hospital on May 1, 1951. He had been in his usual health until September, 1950, when he noted a painful, red, tender

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subcutaneous nodule between the shoulder blades, which lasted about one month and then subsided. Following this he developed increasing generalized weakness. Nodules appeared on the arms, shoulders and anterior abdominal wall, and in the inguinal area. They appeared intermittently, remained tender for from one to three weeks, and subsided. These episodes were associated with an evening temperature elevation. He developed marked anorexia, and between September, 1950, and May,

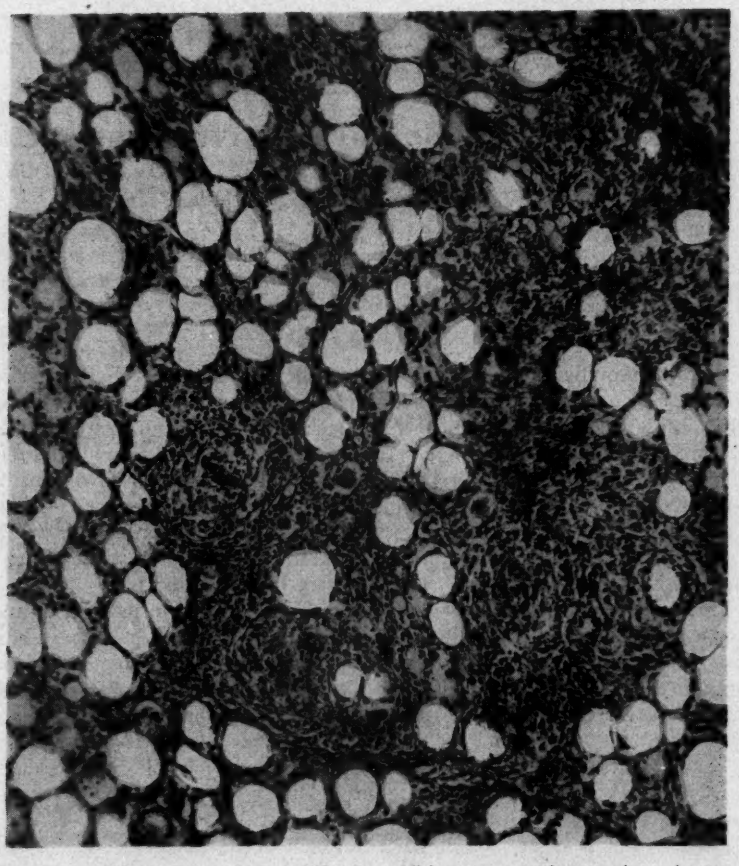

FIG. 1 A. Subcutaneous tissue, ×120. In addition to granulomas, the subcutaneous tissue in other areas shows fibrinoid necrosis of ground substance and arterioles, lymphocytes and histiocytes.

1951, lost 50 pounds. In April, 1951, at another hospital, biopsies of two nodules were reported to show fatty tissue with lymphocytic infiltration and necrosis, compatible with Weber-Christian disease (nonsuppurative panniculitis). Ten x-ray treatments were directed at the nodules and the spleen. System review was unrevealing except for weakness, anorexia, nausea following the x-ray therapy, and dyspnea on exertion since the onset of the present illness.

Past History: The patient had been hospitalized in January, 1949, at Long Beach Naval Hospital for rectal bleeding. An upper gastrointestinal series, gall-bladder series and a barium enema were reported to be normal. While in the hospital the patient developed signs, symptoms and x-ray evidence of a perforated viscus. A perforated jejunal ulcer was resected. The pathology report described a chronic granulomatous reaction with many tubercles, presumed to represent tuberculosis.

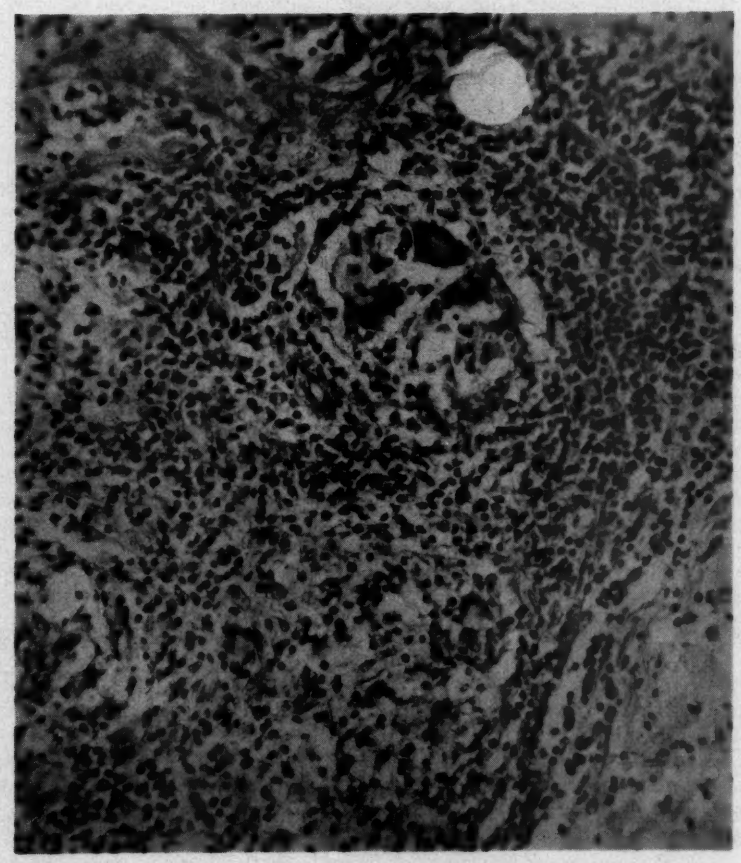

FIG. 1 B. Subcutaneous tissue, ×300. Shows lipogranulomatous reaction with giant cells.

Restudy of these slides shows the granulomatous inflammation of submucosa and serosa, similar to the reaction in the subcutaneous tissues seen in 1951 (figure 1). In 1947 he was told that he had a duodenal ulcer, established by x-ray. In 1941 he had a subtotal thyroidectomy performed. No other significant past medical or family history was obtained. He had not been taking any form of medications and was not an alcoholic.

Physical Examination: Weight, 200 pounds; temperature, 100° F.; pulse, 80; blood pressure, 110/80 mm. of Hg. The patient was obese and appeared chronically ill. There was bilateral fatty gynecomastia. Many moist râles were heard in the left lower lung field posteriorly. The liver was enlarged to three fingerbreadths below the right costal margin, and was smooth and nontender. The tip of the spleen was palpated and nontender. Subcutaneous nodules were located on the right arm, right shoulder and abdomen, and in the inguinal area. They varied in diameter from 1 to 15 cm.; some of the newer lesions were tender. They were all firm, and the overlying skin was atrophic. In the suprapubic area there was a "2 cm. radiation ulcer."

Laboratory Studies: Hematology: White blood cells, 6,100, with 76 polymorphonuclears, 17 lymphocytes, 4 monocytes, 1 eosinophil and 2 basophils; red blood cells, 4.33 million; hemoglobin, 12.8 gm.; sedimentation rate, 17. Urinalysis: specific gravity, 1.025; protein and sugar, negative; 2 to 3 white blood cells per high power field, 1 to 2 red blood cells per high power field. Blood Chemistry: cephalin flocculation, 4 plus; thymol turbidity, 5.5 units; alkaline phosphatase, 7.4 units; cholesterol, 255; esters, 150. Seven blood cultures were sterile. Agglutinins for infectious agents, serologic tests for syphilis, complement fixation for Q-fever, Coombs' test and histoplasmin, coccidioidin and PPD #2 skin tests were either negative or normal.

Chest x-ray on May 2, 1951, revealed increased fibrosis and hilar calcification, with a band of increased density in the left sixth anterior interspace having the characteristics of atelectasis. On repeat x-ray on May 16, 1951, this band of atelectasis had disappeared, but the upper mediastinum appeared slightly widened.

Surgical Biopsy: On May 16, 1951, a nodule on the right forearm and one on the abdomen were biopsied. The pathologic report concurred with the original biopsy revealing a nonsuppurative panniculitis (figure 1).

Hospital Course: The patient had an evening temperature of from 100° to 103° F. every day. He began to complain of epigastric distress. A gastrointestinal series revealed a duodenal ulcer. His stools became persistently positive for occult blood, and the red cell count and hemoglobin fell. Leukopenia was noted. Between May 23 and May 31, 1951, the patient was given three blood transfusions. On June 29, 1951, he was started on ACTH, 5 mg. intravenously. Within 24 hours his temperature became normal and remained so. There was rapid improvement symptomatically. He developed no new nodules, and the previously noted nodules disappeared. His ulcer was adequately controlled with Banthine and Malcogel. On June 28, 1951, a sternal marrow biopsy was reported to show erythroid hyperplasia, but the mechanism of the leukopenia was not evident from this study. On July 26, 1951, ACTH was discontinued. The patient was asymptomatic. On July 30, 1951, he developed dysuria and his temperature began to spike to 103° F. daily. Urine examinations revealed many white blood cells, and a culture of nonhemolytic streptococci, gram-positive rods, *Aerobacter aerogenes* and Sarcina. August 2, 1951, several new nodules were noted, and by August 10, 1951, there were nodules on the arms, legs, back, abdomen and buttocks. Also, on August 10 the patient was noted to be jaundiced. The urine was dark and the stools were clay-colored. Gantrisin and streptomycin produced no effect. On August 15, 1951, Aureomycin was started. On August 20, 1951, a liver biopsy showed parenchymatous degeneration with mild inflammation. On August 26, 1951, his temperature became normal. The nodules began disappearing and the jaundice cleared. He was discharged on October 4, 1951.

Additional Laboratory Studies: Six urine specimens were negative for AFB on culture and guinea pig inoculation. An intravenous pyelogram was normal.

LIVER FUNCTION STUDIES

Date	Cephalin Floc.	Thymol T.	Alk. Phos.	Van den Bergh
5-10-51	4+	5.5	7.4	
6-21-51	4+	5.5	14.0	
8-13-51	4+	10.0	29.0	3.7 mg. 1 min. 7.8 mg. total
8-22-51			26.0	1.8 mg. 1 min. 3.4 mg. total
9-12-51	4+	8.0	3.7	0.8 mg. 1 min. 1.6 mg. total

HEMOGRAM DATA

Date	RBC	Hgb.	WBC	Polys.	Lymphs.	Monos.	Eos.	Baso.	Plat.	Sed. Rate
5-23-51	2.73	9.0	3,800	74	21	4	0	1		55
6-27-51	3.63	9.3	1,050	66	27	7	0	0	100,000	29
7-10-51	4.51	13.2	9,450	84	12	4	0	0	90,000	1
8-14-51	3.74	10.5	3,600	70	26	1	3	0		40
9-25-51	4.29	12.5	2,700	54	44	2	0	0	100,000	
10-2-51	4.19	12.8	5,100	56	34	6	2	2		35

2. *Second Admission:* Present Illness: The patient was seen intermittently in the Out-Patient Department following discharge from the hospital. From time to time nodules were noted on the arms, shoulders and abdomen. In January, 1953, he developed fever, anorexia, a slight cough and moderate dyspnea. His fever was intermittent, but with a daily elevation occasionally as high as 104° F. In March he was seen by his local physician, who placed him on cortisone, without effect. On March 16, 1953, the patient was re-admitted to the hospital.

Physical Examination: The patient was an elderly white male who appeared chronically ill. Temperature, 102° F.; pulse, 76; blood pressure, 164/90 mm. of Hg. Gynecomastia was noted as on the previous admission. There were bilateral basal pulmonary râles. The liver was palpated and felt to be enlarged. There was a moderate amount of voluntary muscle guarding in the epigastrium. No other masses were felt and no tenderness was elicited. Several small subcutaneous nodules, 1 cm. in diameter, were located over the right shoulder and arm and over the lower abdomen. These were nontender.

Laboratory Studies: Hematology: white blood cells, 6,400, with 74 polymorphonuclears and 26 lymphocytes; red blood cells, 4.25 million; hemoglobin, 13.4 gm.; sedimentation rate, 35. Serologic tests for syphilis, blood urea nitrogen, serum electrolytes, urinalysis, and agglutination tests for typhoid-paratyphoid, Brucella and Weil-Felix reactions were either negative or normal. Cephalin flocculation, 3 plus in 48 hours; thymol turbidity, 8.1 units. Bromsulfalein, 31% retention. Urine culture, sterile. Stools, 4 plus for occult blood.

Chest x-ray on March 19, 1953, showed confluent and mottled infiltrations in the lower two thirds of both lung fields. The infiltrations were described as round and discrete. An upper gastrointestinal series on March 19, 1953, revealed constant deformity of the duodenal bulb, although no definite duodenal ulcer could be demonstrated.

Hospital Course: The patient's temperature remained elevated (102° to 103° F.). On March 20, 1953, he suddenly fainted, fell to the floor, and vomited 300 c.c. of clotted blood. The blood pressure was 104/58 mm. of Hg; red blood cells, 2.78 million; hemoglobin, 7.6. In the following 36 hours he was given 11 pints of whole blood. His blood pressure was maintained at levels of 110 to 140 mm. of Hg systolic, and 60 to 70 mm. of Hg diastolic. Pulse ranged from 90 to 112. The hemoglobin remained approximately 9.2 gm. On March 22, 1953, there was no further evidence of bleeding, but there was marked increase in pulmonary râles. On March 23, 1953, the patient was semicomatose. On March 24, 1953, he was more alert. The blood

pressure was well maintained; pulse was quite rapid (120); temperature, 105° F. He was given treatment consisting of penicillin and streptomycin, atropine, Sodium Luminal, Malcogel, Aureomycin, a 16-hour intravenous drip of 5 units of ACTH in 1,000 c.c. 5% glucose and water, and 1.6 mg. of Cedilanid. On March 24, 1953, a state of peripheral vascular collapse developed and the patient died.

B. Autopsy Findings:

1. *Gross Examination:* The body was that of an embalmed, refrigerated 64 year old white male who measured 72 inches and weighed 206 pounds. He was markedly obese, well nourished, well hydrated and well developed. Regional examinations revealed the following significant findings: On the right upper arm laterally there was a subcutaneous fatty nodule approximately 2.5 cm. in diameter which upon incision revealed fatty tissue that was reddish pink compared to the surrounding yellow, uninvolved fatty tissue. It was not demarcated or separable by blunt dissection. There appeared to be a few shotty nodules in the lower extremities, but they were poorly discernible. Over the abdomen there was a thick panniculus. The peritoneal cavity revealed dilated stomach and loops of bowel, and a marked amount of intra-abdominal fat in the mesentery, omentum and other areas. There were fibrous adhesions at the lower edge of the liver and spleen. Intra-abdominal and mesenteric lymph nodes were moderately enlarged, measuring up to 1.5 cm. In the celiac region the similarly enlarged nodes were surrounded by slightly indurated adipose tissue. The mesentery revealed several irregularly shaped calcified nodules, measuring up to 1.5 cm. in greatest dimensions. One of the nodes had a focus of calcification measuring 0.3 cm. at the periphery of the node. The adipose tissue in the periduodenal and peripancreatic areas was also somewhat indurated. The mediastinum was negative.

The musculoskeletal system showed no abnormalities.

Respiratory System: Each lung weighed 800 gm. The trachea and bronchi contained some blood-tinged mucus. The pleural surfaces in the region of the lobal fissures had a few fibrous adhesions, and the pleura was depressed and dull in areas over underlying nodules. The lung parenchyma contained numerous nodules measuring from 0.8 to 3 cm. (figure 2) in greatest diameter. The nodules were in all lobes of both lungs. The region of the right upper lobe was least involved. The nodules were firm and on cut section were grayish pink. The lobular architecture appeared to be preserved. The larger nodules in the central areas had central zones of yellowish, putty-like necrosis. The nodules appeared to be fairly well demarcated from or occasionally blended with surrounding aerated parenchyma. No exudate was expressed from the nodules. The lesions gave the impression of being an organizing granulomatous pneumonitis or an alveolar cell carcinoma; frozen section revealed a monocytoid inflammatory consolidation without carcinoma. The hilar nodes were moderately enlarged and on cut section revealed a grayish lymphoid parenchyma with spotty anthracosis.

Cardiovascular System: The heart weighed 480 gm. The epicardial surface revealed a white "soldier's" plaque over the basilar portion of the right ventricle. There were similar white plaques in the region of the auricles and the posterior right ventricle. The myocardium was soft throughout the left ventricle, including the anterior wall, and the cut sections were brownish red, with preserved architecture. The appearance suggested parenchymatous degeneration. The tricuspid valve on the atrial surface of the medial leaflet revealed an area of pinkish gray, firm granularity measuring 4 cm. in greatest dimension and suggesting a healed fibrous valvulitis. On the medial leaflet of the mitral valve, atrial surface, there were three similar but punctate granular deposits. The aorta revealed a moderate amount of atherosclerosis with atheromatous deposits; in the iliac region and below the renal veins there were foci of calcification.

Hemic and Lymphatic Systems: The spleen weighed 550 gm. The capsule had a few omental adhesions. The cut section revealed a soft red splenic pulp with poorly identifiable follicles. Lymph nodes were as described above. Bone marrow and blood were negative.

Digestive System: The stomach contained approximately 800 ml. of bloody and blood-clotted material. The duodenum on the posterior wall had a penetrating ulcer measuring 1.5 cm. in diameter, in the center of which there was a small thrombosed artery. There were fibrous adhesions between the serosal aspect of the ulcer and the head of the pancreas in the fatty zone. There was a moderate amount of blood in the second portion of the duodenum, the jejunum and the colon; there were ap-

FIG. 2. Segments of lungs (fixed tissue). Note indiscrete and demarcated nodules replacing lung parenchyma.

proximately 1,000 ml. of blood in the small and large intestines. The pancreas weighed approximately 175 gm., and the cut sections revealed fatty infiltration, especially in the head region. The liver weighed 1,950 gm., and was firm, grayish yellow and moderately lobulated. The capsular surface had a few omental adhesions. The cut sections revealed small pseudonodularities. These nodules were pale yellow, with exaggerated gray, depressed trabecular markings, evidencing a fatty liver with cirrhosis.

Urogenital System: Essentially negative.

Endocrine System: The thyroid was notably small and fibrous; in the region of the right lobe there were some irregular nodular areas, apparently representing a residual of the previous thyroidectomy. The adrenals were usual in size; the cortex measured approximately 0.15 cm. thick and was yellow and lipoid-like rich. The pituitary and parathyroids showed no abnormalities.

Nervous System: The brain weighed 1,550 gm., and the basilar cerebral arteries showed fairly marked atherosclerosis. Filling the entire left cerebellar pontine angle was an encapsulated yellow fatty mass measuring 1.5 cm. in diameter, the surface of which was compressed and flattened. This lesion was interpreted as a lipoma of the leptomeninges which did not cause compression of the underlying brain tissue.

2. *Microscopic Findings:* Miscellaneous: In addition to the granular and hyaline calcific areas, the mesenteric nodules showed bony metaplasia surrounded by adipose

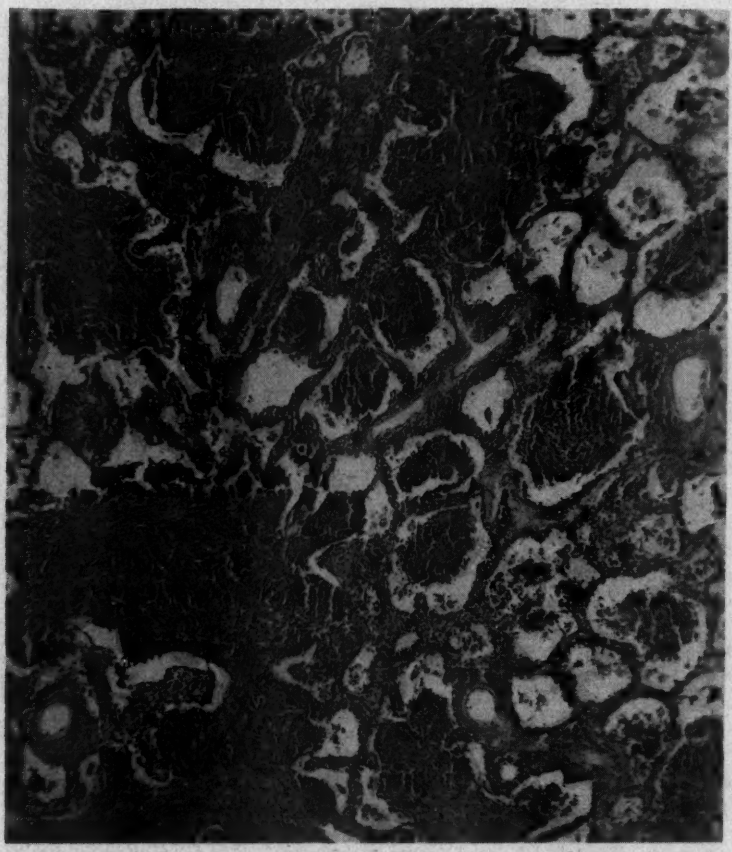

FIG. 3 A. Lung, × 66. Shows organizing fibrinous exudate filling and bridging alveoli.

tissue. In the mesenteric and peripancreatic adipose tissue there were focal areas of young granulation tissue replacing destroyed fat lobules.

Integumentary System: The subcutaneous tissue showed slight changes, including interstitial hemorrhage, coarse granular fibrinoid necrosis involving the interstitium and arterioles, and lymphocytes with polymorphonuclear leukocytes and a few macrophages (considered to be the earliest change in panniculitis [7]).

Musculoskeletal System: No significant findings.

Respiratory System: The nodular densities in the lungs consisted of fibrinous, granular debris filling and bridging alveoli, frequently with young fibroblasts, and a mild admixture of inflammatory cells, including polymorphonuclear leukocytes, lymphocytes and histiocytes, many of them lipid-filled (figure 3 A). In other areas the alveoli were filled with large, lipid-containing histiocytes and a few leukocytes (figure 3 B). Here there were partially epithelialized alveolar walls and foci of organizing

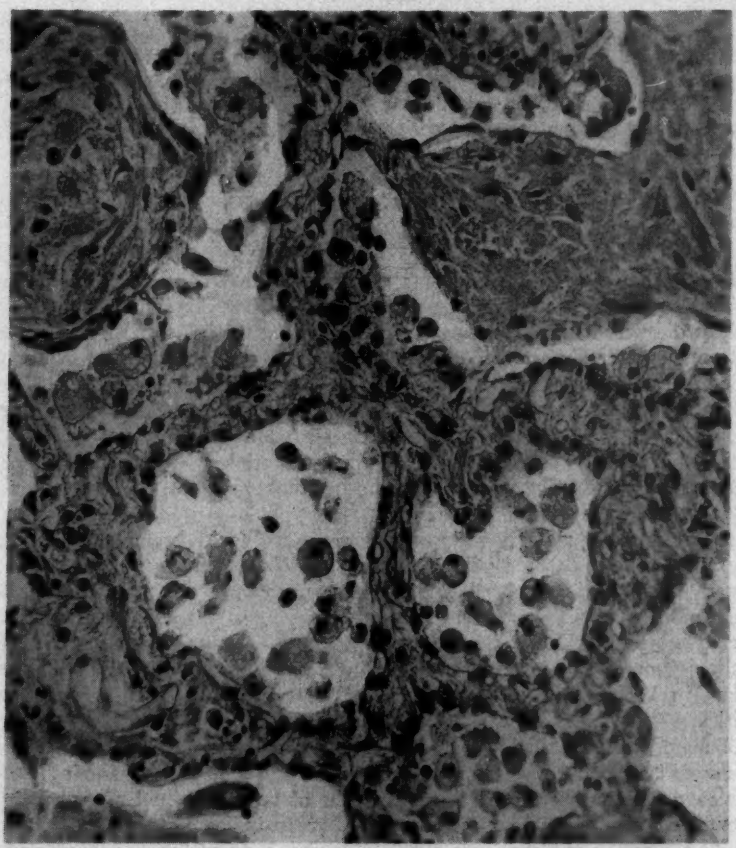

FIG. 3 B. Lung, ×300. Shows lipid histiocytes in partially epithelialized alveoli, and organizing fibrinous material bridging alveoli.

fibrinoid exudate. The alveolar walls were thickened. The fibrinoid material filling the alveoli was diffusely PAS-positive, and the lipid-filled histiocytes were Sudan IV-positive; the Masson trichrome stain revealed threadlike connective tissue staining in some areas. In subpleural locations there were admixtures of lipid-filled histiocytes, leukocytes and fibrinous exudate. In addition, there were several areas of recent bronchopneumonia in which the bronchioles and adjacent alveoli were filled with segmented neutrophils.

Cardiovascular System: The mitral valve revealed a small fibrohyaline thickening of the free margins, with a peripheral layer of fibroblasts in a suggestive palisading configuration. The tricuspid valve revealed a somewhat similar small nodule, although more hyaline in character. There was mild interstitial edema of the myocardium.

Hemic and Lymphatic Systems: The spleen revealed a focus of hemorrhage with surrounding fibrosis. There was an increase of collagen in the red pulp, and little white pulp. The lymph nodes in the celiac region showed areas of lipogranulomas consisting of globules of fat, fibrinoid debris and many mononuclear cells. In the surrounding adipose tissue there were small collections of histiocytes and plasma cells.

Digestive System: In the liver there was a mild form of portal cirrhosis. The periportal connective tissue was increased, producing a pseudolobular nodular formation. The hepatic cells were swollen, and many were replaced by fat globules. The duodenum revealed a penetrating ulcer crater having a base of granulation tissue with a thrombosed, thick-walled artery.

Urogenital System: No significant findings.

Nervous System: A section of a leptomeningeal lipoma revealed well formed fat without an inflammatory component.

Discussion

This case, which clinically represented the Weber-Christian syndrome, was confirmed by subcutaneous biopsies. Necropsy revealed the earliest minimal acute manifestation of panniculitis in the subcutaneous tissue [7] and evidence of healed and active chronic lesions in the adipose tissue of the omentum, mesentery and retroperitoneum. The cirrhotic liver has been noted in other reported autopsy cases, and might possibly be a morphologic component of Weber-Christian syndrome.[2, 3] It is difficult to evaluate etiology or pathogenesis of the liver pathology in our case because serum hepatitis may have been an underlying factor in the production of the cirrhosis.

All attempts at providing clues or evidence for an etiologic agent, especially tuberculosis, were to no avail in our case of Weber-Christian syndrome. Innumerable slides of premortem and postmortem material were negative for acid-fast bacilli, as were antemortem cultures and guinea pig inoculations of urine. During life the PPD #2 skin test was negative. Reëxamination of the slides of the jejunum revealed a granulomatous process compatible with lipogranulomata in Weber-Christian syndrome, or with lipogranulomata of nonspecific entities.

The most interesting aspect of this case was the unusual granulomatous pneumonitis, which seemed to constitute a lipogranulomatous organizing exudate with moderate numbers of lipophages. The associated, frankly purulent, acute terminal bronchiolar pneumonia in other areas indicated that the lipogranulomatous fibrinous process was not a cortisone-modified inflammatory response to a common infectious agent. The persistent search for microbiologic components of the granulomas in numerous tissue sections was unsuccessful, whereas bacteria were seen in the acute focal purulent pneumonic areas. Since there was no history of exposure to exogenous lipids, the lipogranulomatous lung lesions were considered to be endogenous lipogranulomas.

The celiac lymph nodes showed an unusual fibrinous lipophagic reaction, with a similar reaction in the surrounding adipose tissue.

Although Weber-Christian syndrome may be a disease of a specific etiology, none could be identified in this case, or consistently identified in other cases.

That it could be due to an uncommon infectious agent, such as a viral, rickettsial, bacterial or other microbiologic agent not readily identified or discovered as yet, cannot be denied as a possibility. The association with diseases of known etiology but difficult of diagnosis, such as brucellosis, tuberculosis, leprosy,[8] etc., with an unusual tissue reactivity, is possible and is reported in the literature; but any of these agents as the particular, specific etiologic agent is unlikely in view of the numerous negative studies in this and other cases. The fact that the etiology is unknown and that the manifestations of panniculitis have been associated in individuals with numerous etiologic possibilities has led to its designation as a syndrome. It is a structural reaction manifested in association with infectious agents or other etiologies.

The over-all pathology illustrated in this case suggests that the common denominator in the pathogenesis of the lesions associated with Weber-Christian syndrome may well be related to an interstitial reaction to an abnormal lipoprotein, or a response of sensitized fat cells, or a resultant of increased capillary permeability, etc. The lung lesions in this case suggest that the reaction can occur in areas other than adipose tissues. It is not known what initiated the focal manifestations in the lung, but it might have been related to shock and focal infection. In the future it might be interesting and revealing if patients with Weber-Christian syndrome were studied for interstitial sensitivity reactions to blood lipoproteins (skin, or subcutaneous injections), and if blood lipoprotein electrophoretic studies were done. In the past, other blood lipoprotein centrifugation studies (Gofman indices)[7] and blood lipid studies have shown no abnormalities.

Summary

This is a case report, including autopsy findings, of a 64 year old white male with a granulomatous lesion of the jejunum, and clinical and biopsy diagnoses of nonsuppurative nodular relapsing febrile panniculitis (Weber-Christian syndrome), who developed an unusual nodular endogenous lipid granulomatous pneumonitis and had a terminal hemorrhage from a chronic duodenal ulcer. It is considered that the granulomatous lesion of the jejunum and the granulomas of the lung were visceral manifestations of the Weber-Christian syndrome in this case. Comments on pathogenesis and future study of Weber-Christian syndrome are presented. It is suggested that a lipoprotein interstitial sensitivity reaction might explain the pathogenicity of the varied visceral and adipose tissue manifestations in Weber-Christian syndrome associated with diseases of known and unknown etiology.

Addendum

The unusual nodular lipid-fibrinous pneumonitis in the patient reported in this paper is similar pathologically to 27 cases reported in the article "Pulmonary Alveolar Proteinosis," by Rosen, S. H., Castleman, B., and Leibow, A. A., in the New England J. Med. **258**: 1123, 1958. They report no clues as to pathogenesis. This case with Weber-Christian's syndrome should add some thought to this interesting pulmonary disease entity.

Summario in Interlingua

Recidivante non-suppurative panniculitis febrile nodular (syndrome de Weber-Christian) es un incommun entitate clinic. Como causa de morte illo es rar. Le litteratura ha circa 10 reportos de casos mortal.[1, 2, 3, 4] In le casos in que le morte

esseva attribuite a panniculitis systemic, le necropsia ha revelate extense affectiones de histo adipose, incluse le panniculo e/o, in certe casos, le histo adipose mesenteric, omental, e retroperitonee, le medulla ossee,[5] e histo adipose del visceres—per exemplo le submucosa del intestinos.

Le presente articulo es un reporto del caso—incluse le constatationes necroptic—de un masculo de racia blanc de 64 annos de etate con un lesion granulomatose del jejuno e diagnoses clinic e bioptic de recidivante non-suppurative panniculitis febrile nodular (syndrome de Weber-Christian) qui disveloppava un inusual typo de endogene pneumonitis lipido-granulomatose nodular e qui suffreva terminalmente un hemorrhagia ab chronic ulcere duodenal. Al tempore del necropsia, le panniculitis subcutanee esseva vidite in un area con le plus precoce minimo de alterationes, e panniculitis active e resanate esseva notate in le histo adipose del region mesenteric. Es opinate que le lesion granulomatose del jejuno e le granulomas del pulmon in iste caso es manifestationes visceral del syndrome de Weber-Christian. Es presentate commentos relative al pathogenese e al studio futur del syndrome de Weber-Christian. Es opinate que un reaction de sensibilitate interstitial a lipoproteina esserea adequate como explication del pathogenicitate del varie manifestationes de histo visceral e adipose in casos de syndrome de Weber-Christian que es associate con morbo de etiologia cognoscite e incognoscite.

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3. Anthony, J. E., Jr., and Davidson, J. K., III: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian's disease): report of a case with autopsy findings, J. M. A. Georgia **42**: 138, 1953.
4. Ritama, V., and Trusius, F. E.: Generalized lipogranulomatosis (Weber-Christian's syndrome), report of a case with autopsy, Ann. med. int. Fenniae **42**: 133, 1953.
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6. Beerman, H.: Weber-Christian syndrome, Am. J. M. Sc. **225**: 446, 1953.
7. London, S. B., and Lev, M.: Acute relapsing panniculitis; report of a case of Weber-Christian disease with vascular changes, Arch. Int. Med. **92**: 750, 1953.
8. Birrell, J. H. N.: A note on leprosy as an etiological factor in the Weber-Christian syndrome, M. J. Australia **2**: 7, 1953.

EDITORIAL

RESEARCH IN ARTERIOSCLEROSIS—THE FIRST FIFTY YEARS

THE year 1958 marks the fiftieth anniversary of the first successful experimental study of arteriosclerosis, the greatest killer of our century. The first experiment on tuberculosis had been completed forty years previously. Villemin's demonstration of tuberculosis in rabbits inoculated with human material made possible the isolation of the bacillus by Koch, and all subsequent studies of host sensitivity, diagnostic and therapeutic methods. It marked the beginning of the end of tuberculosis as an uncontrollable plague of city dwellers.

When Ignatovski, of the Russian Imperial Military Medical Academy, reported in 1908 that rabbits fed milk and egg yolk developed severe arteriosclerosis,[1] he gave mankind the key to control of a disease which was rapidly becoming more prevalent as living standard rose and infectious disease killed fewer people. The experimental technic he introduced was wisely exploited by his colleagues in the Academy. Stuckey found that neither fish-oil, meat nor sunflower-seed oil caused arterial lesions, while egg yolk and brain were more effective than milk.[2] Wesselkin and Chalatov showed that cholesterol-rich foods caused cholesterol-rich deposits in tissues. N. N. Anichkov and Chalatov, in 1914, produced lesions by adding pure cholesterol to rabbit food.[3] Anichkov early emphasized the fact that hypertension and other factors accelerated the vascular lesions. He is still active in this field, and his pupils have made important contributions in the last decade, recently summarized in English by Myasnikov.[4]

Although confirmation of Anichkov's experiment with cholesterol was promptly reported by Bailey of Stanford University,[5] two decades passed before Timothy Leary of Boston repeated them and tried to convince clinicians that these results fitted his observations on the relation of arteriosclerosis to diet in various social strata.[6] It was the difference in diet and in severity of arterial lesions in the rich and poor, in officers and soldiers, and in milk-drinking pastoral tribes and in peasants living on vegetables and grain which had inspired Ignatovski to try an experimental attack on

[1] Ignatovski, A. I.: On the influence of animal food on the tissues of the rabbit. Reports of the Imperial Military Medical Academy, Saint Petersburg **16**: 154, 1908.

[2] Stuckey, N. W.: On changes in the aorta of the rabbit due to feeding with different types of fat, Centralbl f. allg. Path u. path. Anat. **23**: 910, 1912.

[3] Anichkov, N., and Chalatov, S.: On experimental cholesterol steatosis and its significance in the development of various pathologic processes, Centralbl. f. allg. Path u. path. Anat. **24**: 1, 1913.

[4] Myasnikov, A. L.: Influence of some factors on development of experimental cholesterol atherosclerosis, Circulation **17**: 99, 1958.

[5] Bailey, C. H.: Atheroma and other lesions produced in rabbits by cholesterol feeding, J. Exper. Med. **23**: 69, 1916.

[6] Leary, T.: Atherosclerosis, the important form of arteriosclerosis, a metabolic disease, J. A. M. A. **105**: 475, 1935.

the problem. Recent and very extensive studies, in Central [7] and North America,[8] in Africa,[9] Europe, the Near East,[10] Japan and Hawaii [11] have fully confirmed the correctness of the basis for Ignatovski's hypothesis—men who consume eggs and milk regularly do have higher blood cholesterol levels, more severe arterial lesions, and higher death rates from coronary disease than men who have little animal or dairy fat in their diets.

In recent experimental studies with rabbits, the Russians [4] confirmed what has long been known to be true in the human race. On the same diets some individuals or strains show blood cholesterol levels much lower or higher than the average. Also, with similar elevations of blood cholesterol, there may be considerable variation in severity of aortic or coronary lesions. In cholesterol-fed rabbits, levels of blood cholesterol and severity of aortic disease were reduced by such drugs as barbiturate, while benzedrine and caffeine had the opposite effect.[4] Ascorbic acid reduced and vitamin D augmented the effects of cholesterol feeding.[4] But on the average, cholesterol-fed rabbits, like milk- and egg-fed men, have higher blood cholesterol levels and far more severe lesions in the arteries than rabbits or men who eat only vegetables.

A striking difference between the rabbit (or the chick which has proved equally sensitive to cholesterol feeding) and the higher mammals was first clearly defined by the experiments of Li and Freeman, in 1946.[12] Prior to that time it was generally realized that plasma cholesterol levels in man rose relatively little when cholesterol-rich foods were added to the diet, and that dogs, cats and rats could not replace rabbits in the Anichkov experiment. Li and Freeman found that while neither cholesterol feeding nor high fat diet had appreciable effects on plasma cholesterol in dogs, a diet rich in fat and cholesterol had a most decided effect, and the plasma level rose even higher if the diet was deficient in protein. Experiments by many investigators have gradually made it apparent that rabbits and chicks absorb cholesterol efficiently on diets low in fat, but dogs, monkeys and men do not absorb much biliary or dietary cholesterol unless the diet contains sufficient fat. In man, the bile provides daily as much cholesterol as would 5 to 10 eggs [13] and the absorption of this is increased when the diet is rich in animal fat.

[7] Mann, G. V., Munoz, A., and Scrimshaw, N.: The serum lipoprotein and cholesterol concentrations of Central and North Americans with different dietary habits, Am. J. Med. **19**: 25, 1955.

[8] Hardinge, M. G., and Stare, F. J.: Nutritional studies of vegetarians. Dietary and serum levels of cholesterol, J. Clin. Nutr. **2**: 83, 1954.

[9] Bronte-Stewart, B., Antonis, A., Eales, L., and Brock, J.: Effect of feeding different fats on serum cholesterol, Lancet **1**: 521, 1956.

[10] Toor, J., Katchalsky, A., Agman, J., and Altaloref, D.: Serum lipids and atherosclerosis among Yemenite immigrants in Israel, Lancet **1**: 1270, 1957.

[11] Keys, A., Kusakawa, A., Bronte-Stewart, B., Larson, M., and Keys, M. D.: Lessons from serum cholesterol studies in Japan, Hawaii, and Los Angeles, Ann. Int. Med. **48**: 83, 1958.

[12] Li, T. W., and Freeman, S.: Experimental lipemia and hypercholesterolemia produced by protein depletion and by cholesterol-feeding in dogs, Am. J. Physiol. **145**: 660, 1946.

[13] Stanley, M. M., and Cheng, S. H.: Cholesterol exchange in the gastrointestinal tract in normal and abnormal subjects, Gastroenterology **30**: 62, 1956.

In all warm-blooded vertebrates, plasma cholesterol rises steeply on diets rich in saturated fats and in cholesterol. In some species, such as the chick and rabbit, cholesterol rises markedly when cholesterol alone is added to a vegetable diet. In others, such as man and the dog, adding cholesterol to the diet has minimal effect on the blood level, which rises when saturated coconut oil replaces corn oil in a cholesterol-free diet.[14] But even in rabbits, replacing corn oil with saturated coconut oil causes a marked rise in blood cholesterol and leads to atherosclerosis.[15] Saturated fat acts, as shown in isotope studies by Ahrens and Hellman,[16] by a reduction of fecal sterol loss as compared by that on unsaturated fat in the diet. It may do this by decreasing biliary production or increasing enteric absorption. Ignatovski, guided by clinical experience, chose foods rich in saturated fat and cholesterol and poor in unsaturated fat because they were most strikingly abundant in the diets of rich Russians as contrasted with the poor. His choice was correct, even though his idea that the protein of these foods was harmful proved to be wrong. Recent work shows that no foods surpass eggs and butter fat in raising blood cholesterol of rabbits or men, and none have more striking effects in accelerating thrombus formation.[17]

The importance of unsaturated fat in protection against arteriosclerosis was first suggested in 1941 by I. Snapper, contrasting the diets and the incidence of vascular lesions in Holland and in North China.[18] That such fats lower blood cholesterol was proved by Groen, of Holland,[19] and quite independently by Kinsell in California.[20] Probably the most convincing experiments are those of Ahrens on men,[21] and of Stare, on Cebus monkeys.[22] Monkeys on cholesterol-enriched diets had higher plasma levels when corn oil replaced carbohydrate to provide 45% rather than 10% of calories, but the rise was twice as great when lard replaced corn oil.

In view of the fact that Ignatovski's experiments were directed to a

[14] Ahrens, E. H., Jr.: Nutritional factors and serum lipid levels, Am. J. Med. **23**: 928, 1957.

[15] Lambert, G. F., Miller, J. P., Olsen, R. T., and Frost, D. V.: Hypercholesterolemia and atherosclerosis produced in rabbits by purified high fat rations devoid of cholesterol, Proc. Soc. Exper. Biol. and Med. **97**: 544, 1958.

[16] Hellman, L., Rosenfeld, R. S., Insull, W., Jr., and Ahrens, E. H., Jr.: Regulation of plasma cholesterol levels by fecal sterol excretion, Circulation **16**: 497, 1957.

[17] Scott, R. F., and Thomas, W. A.: Methods for comparing effects of various fats on fibrinolysis, Proc. Soc. Exper. Biol. and Med. **96**: 24, 1957.

[18] Snapper, I.: Chinese Lessons to Western Medicine, 1941, Interscience Publishers, Inc., New York, pages 30, 160.

[19] Groen, J., Tjong, B. K., Kamminga, C. E., and Willebrands, A. F.: The influence of nutrition, individuality and some other factors, including various forms of stress on the serum cholesterol, an experiment of nine months duration in 60 normal human volunteers, Voeding **13**: 556, 1952.

[20] Kinsell, L. W., Partridge, J., Boling, L., Margen, S., and Michaels, G.: Dietary modification of serum cholesterol and phospholipid levels, J. Clin. Endocrinol. **12**: 909, 1952.

[21] Ahrens, E. H., Jr., Blankenhorn, D. H., and Tsaltas, T. T.: Effect on human serum lipids of substituting plant for animal fat in diet, Proc. Soc. Exper. Biol. and Med. **86**: 872, 1954.

[22] Portman, O. W., Hegsted, D. M., Stare, F. J., Buno, D., Murphy, R., and Sinisterra, L.: Effect of the level and type of dietary fat on the metabolism of cholesterol and beta lipoprotein in the Cebus monkey, J. Exper. Med. **104**: 917, 1956.

study of arteriosclerosis, and that the clinical observations which fired his imagination were not guided by plasma cholesterol determination, it is surprising to note in the papers of Ahrens and of Stare that the reader is warned not to apply the findings to the problem of atherosclerosis. After Leary, the Americans who produced hypercholesterolemia and atherosclerosis in rabbits and chicks, by cholesterol feeding, insisted on warning, as lately as 1955, that the animal results cast no light on the effects of diet on plasma cholesterol in man. It is now clear that such caution was wise, as far as simple cholesterol feeding was concerned, but it does not apply to the Russian experiments with egg and brain supplements, for these foods are rich in saturated fat as well as cholesterol.

It is necessary to realize that hereditary differences in metabolism [23] and in endocrine and nervous response to stress [24] modify the effects of diet on blood cholesterol, and that sex and heredity modify the relative susceptibility of coronary arteries to atherosclerosis at any given level of plasma cholesterol.[25] But there is no reason to doubt that diet and elevated levels of blood cholesterol affect the arteries of men in the same way as they affect those of rabbits, chicks, dogs and monkeys. And if a diet rich in eggs or butter increases coagulability of human blood, and delays fibrinolysis, there is no reason to doubt that this is related to coronary thrombosis in young men eating diets rich in these foods, or to the myocardial and renal infarcts of rats fed cholesterol and butter fat.[17]

The most convincing proofs that diet does cause human coronary disease are Lober's study of severity of lipid infiltration of coronary arteries from birth to old age,[26] and the Armed Forces Institute of Pathology's report on the coronary arteries in the youthful war dead in Korea.[27] Lober's data show that the greatest annual change in infiltration of the intima occurs in the first year of life; this confirms Bragdon's finding of cholesterol deposition in the intima of suckling rabbits.[28] The annual increase in coronary lipid is also high between the ages of 15 and 30, and only at this time is it much greater in males than females. The Korean material showed atheromas grossly visible in 50% of the coronaries of Americans, average age 22 years. In 10% of these young men, with the world's highest egg and milk intake, thanks to Army diet and to milk shakes and ice cream in the PX of all installations behind the front, one coronary artery had its lumen reduced more

[23] Osborne, R. H., and Adlersburg, D.: Serum lipids in adult twins, Science **127**: 1294, 1958.

[24] Friedman, M., Rosenman, R. H., and Carroll, V.: Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress, Circulation **17**: 852, 1958.

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[26] Lober, P. H.: Pathogenesis of coronary sclerosis, A. M. A. Arch. Path. **55**: 357, 1953.

[27] Enos, W. F., Holmes, R. H., and Beyer, J.: Coronary disease among United States soldiers killed in action in Korea, J. A. M. A. **152**: 1090, 1953.

[28] Bragdon, J. H.: Spontaneous atherosclerosis in the rabbit, Circulation **5**: 641, 1952.

than 50% by atheroma. On the other hand, the Korean and Chinese soldiers, eating no milk products and little egg or meat fat, had no lipid in their coronary intimas.

In relation to Lober's data on the intimal thickening which occurs in boys much more rapidly than in girls in the second decade of life, one must note the evidence from dietary surveys [29, 30] that while American boys greatly increase their intake of eggs and dairy fats between 10 and 15, and continue on high levels for another decade, girls actually consume less of these foods between 12 and 25 than they did in childhood. The differential in atherogenesis in the sexes in adolescence is paralleled by an equally striking difference in ingestion of saturated fats. No one reading these papers can doubt that Ignatovski's main hypothesis was correct. Men, like rabbits, develop atheromas only when diet permits elevation of blood cholesterol, and most men, on diets rich in animal fat, will show lesions similar to those of rabbits fed butter fat or egg yolk.

Even bolder than Ignatovski's trial of these foods in animal experiment, was Anichkov's test with cholesterol. Since it had long been known that mammals produce cholesterol abundantly even on cholesterol-free diets, nothing could have seemed less likely than that cholesterol absorbed from the bowel would cause arterial disease. Anichkov's proof that this is the case has been fully confirmed, the final touch coming from the isotope studies on effects of corn oil and butter fat on plasma and fecal sterol balances.[16] Since this revolutionary idea had no inspiration outside Russia, and fifty years passed without its gaining acceptance throughout the world, it must be regarded as one of the most original in the history of science. Yet the fact that men do not react to pure cholesterol in the same way as rabbits, although they respond alike to butter fat and egg yolk, helped to retard acceptance of Ignatovski's thesis that rich food caused arteriosclerosis in man.

There is today great resistance to the acceptance of any relation of diet to coronary disease. There were good reasons why Priestly, who contributed so much to the final step taken by Lavoisier, never accepted Lavoisier's theories on combustion and metabolism and died a believer in phlogiston. There were good reasons why Virchow, who contributed so much to the study of pathogenesis of disease, was most reluctant to accept Villemin's and Koch's views on infection as a cause of phthisis. During the eighteenth and nineteenth centuries the importance of poor heredity, stressful ways of life (sexual-artistic, not socio-economic!), and poor diet as causes of consumption were perfectly obvious to all, while the slow subtle process of primary infection, latency, and apical cavitation were not easily understood.

[29] Young, C. M., and Pilcher, H. L.: Nutritional status survey, Croton Township, N. Y. II. Nutrient usage of families and individuals, J. Am. Diet. Assoc., Oct. 1950, 776–781.

[30] Eppright, E. S., and Swanson, P. P.: Distribution of calories in diets of Iowa school children, J. Am. Diet. Assoc. **31**: 144, 1955.

Cavitation and ulceration dominated thinking, long after miliary lesions were noted in man and produced in animals.

Today thrombosis dominates much of the thinking about coronary disease. Duguid [31] and Morgan [32] consider thrombosis as primary, just as Virchow considered degeneration of tissue the primary factor in phthisis. Others emphasize the role of heredity [22] or of socio-economic stress [24, 33] in causing the disorder or in precipitating the onset of symptoms, just as these factors were formerly stressed by all students of tuberculosis, and recently have been reemphasized. Some families do have low blood cholesterol levels and little arterial disease on diets which lead to precocious onset of trouble in many. This is true in some strains of rabbits also, and in no way disproves the importance of diet as the essential factor, which some resist better than others. Stress does raise blood cholesterol, but 20 years of war and revolution, stressing the Koreans and Japanese, have led to no such widespread atherosclerosis at age 20 as was noted in the American soldiers, who scarcely knew what "socio-economic stress" meant. Diet (or Koch's bacillus) is not the only factor in determining if and when we die of coronary disease (or apical cavitation), but diet rich in saturated fat (or exposure to *M. tuberculosis*) seems to be the one all-important cause of the disease.

Another reason to object to diet as an important cause of coronary disease is the fact that there is not a perfect fit, in all parts of the world, between dietary habits and coronary death rates,[34,35] or between rising death rates and rising consumption of animal fat. These objections deserve consideration, since they may cast additional light on the role of race, of exercise and other factors on lipid metabolism and coronary disease. The countries with high fat intakes and not so high coronary death rates, at least in Europe, are countries where the bicycle riders greatly outnumber the automobile owners and those who go to work on buses or subways. Some are lands where beer-drinking and sobriety, as well as high fat intake, are the rule. These apparent exceptions to the general rule should not lead us to ignore the outstanding trend in the relation of diet and arterial disease, nor to throw out extensive animal studies which prove a constant relation of diet to atherogenesis in many species. In man, blood cholesterol varies with the saturated fat content of the diet, just as in rabbits. In the latter, atherogenesis follows. Since the most rapid deposition of intimal lipid in man occurs during suckling and when adolescent American boys are gorging on animal fat, are not animal experiments relevant?

[31] Duguid, J. B., and Robertson, W. D.: Mechanical factors in atherosclerosis, Lancet 1: 1205, 1957.

[32] Morgan, A. D.: The Pathogenesis of Coronary Occlusion, 1957, C. C Thomas, Springfield, Ill.

[33] Russek, H. I., and Zohman, B. L.: Relative significance of heredity, diet and occupational stress in coronary heart disease, Am. J. M. Sc. 235: 266, 1958.

[34] Yerushalmy, A., and Hilleboe: Fat in the diet and mortality from heart disease, New York State J. Med. 57: 2343, 1957.

[35] Yudkin, J.: Diet and coronary thrombosis—hypothesis and fact, Lancet 2: 1957, 155.

The experiments performed in the Military Medical Academy which led to our present knowledge are remarkable in many ways. Others had tried to produce lesions by feeding spoiled meat and supposedly toxic material, but Ignatovski chose foods which were considered particularly pure and nutritious. The speed with which the original error, implicating protein, was corrected by other members of the team, and the final satisfying of Koch's postulate by giving experimental animals a pure substance found in the lesions, were noteworthy achievements. The proof that disease may be due to absence of specific substances, the vitamins, had only been accepted by practical people, such as old wives who used cod-liver oil and seafaring men who used lime-juice, and was considered unlikely by professors in 1908. The idea that fatal disease could be due to too much of the good things in the diet was truly revolutionary. Thus the early work of Anichkov bears comparison with that of Harvey on the circulation and of Lavoisier on respiratory exchange of oxygen and carbon dioxide. Universally accepted ideas were disproved, new thoughts were advanced, and intense antagonisms had to be overcome before they won acceptance. Only if physicians accept the facts made clear by the decisive studies of recent years can the full benefits of the work of Ignatovski and Anichkov lead to a decline in disability and death from arteriosclerosis comparable to the decrease in tuberculosis which followed the work of Villemin and Koch.

Today scientific progress is often linked to forms of government and Americans have been soothed by the belief that only in democracies can science and technics develop successfully. It is worth emphasizing that Harvey, Lavoisier and Ignatovski all worked under autocratic regimes in the hands of weak tyrants. Their great discoveries were made just before the revolutions in which their kings were killed. In all three revolutions, strong but even more autocratic regimes were installed. Harvey's home was sacked by the rebels, Lavoisier was beheaded, but the Russian scientists found the new regime friendly and anxious to develop basic research. Under Czars and Party Secretaries, Russian support for art and science, in relation to national wealth, has far exceeded that in most democracies. The results were admirable long before satellites in the sky astonished those who had failed to realize that Russian scientists and technicians were gifted, energetic, and commanded respect and support. That lesson was quite plain to the physicians who knew the history of research in arteriosclerosis.

WILLIAM DOCK, M.D.

DIAGNOSES OF CASES PRESENTED AT CLINICAL-PATHOLOGICAL AND BASIC SCIENCE CONFERENCES, THIRTY-NINTH ANNUAL SESSION, 1958

The Editor has recently received from Dr. Milton Ackerman the following resumé of the diagnoses of the cases presented at these Conferences. It is believed these will be of interest to many of our readers.

I. Clinical Pathological Conference:

Moderator—J. D. Myers, M.D., Professor of Medicine, University of Pittsburgh.

A. Clinical Diagnoses:

1. Myocarditis, diffuse, as hypersensitivity reaction to helminthiasis, particularly ascariasis.
2. ? Diffuse hypersensitivity angiitis.

B. Pathological Diagnoses:

Myocarditis, parasitic type.
Endocardial elastomyofibrosis, inflow tracts, right and left ventricles.
Myocardial hypertrophy, excentric.
Atherosclerosis of coronary arteries, focal, severe.
Mural thrombus, left ventricle.
Chronic passive congestion of lungs, liver and spleen.
Pulmonary infarcts, RML.
Hyperplasia of bone marrow, principally granulocytic.
Chronic pyelonephritis, mild.
Focal pancreatitis.
Purpura, diapedesis type.

II. Clinical Pathological Conference:

Moderator—M. J. Small, M.D., Chief, Tuberculosis Service, Veterans Administration Hospital, East Orange, New Jersey.

A. Clinical Diagnoses:

1. Hospital diagnoses—Adenocarcinoma of the rectosigmoid with metastases to lungs.
2. Dr. Epstein's diagnosis—Metastatic carcinoma of lung, most likely of primary renal origin, and possible fungus disease.
3. Dr. Rabin's diagnosis—Phthisis nigra.

B. Pathological Diagnoses:

1. Adenocarcinoma of the sigmoid colon, well differentiated.
2. Pneumoconiosis (phthisis nigra) involving all lobes of the lungs with:
   a. Cavitation;
   b. Pulmonary fibrosis, advanced;
   c. Pulmonary emphysema, moderate.
3. Bronchopneumonia, recent, all lobes of the lung.

III. Basic Science Conference—Metabolic Disease of Bone:

A. Diagnosis established on first case was parathyroid adenoma.

B. Diagnosis on second case was multiple myeloma.

IV. Basic Science Conference—Jaundice:

A. Diagnosis on first case was carcinoma of the ampulla of Vater.

B. Diagnosis on second case was neuroblastoma of the right adrenal with common duct obstruction.

C. Diagnosis on third case was primary biliary (cholangiolitic) cirrhosis.

V. Clinical Pathological Conference: (Case 1)

Moderator—John V. Straumfjord, M.D., Research Associate, Department of Biochemistry, University of Oregon Medical School.

A. Clinical Diagnoses:

Intra-abdominal malignancy.
Bronchopneumonia.

B. Anatomic Diagnoses:

Amyloidosis, primary, aorta and small arteries, widespread in all organs.
Bronchopneumonia, bilateral.
Emphysema, moderate, bilateral.
Diverticula, multiple, descending colon.
Encephalomalacia, basal ganglia, minimal.

VI. Clinical Pathological Conference: (Case 2)

Moderator—Harold Jeghers, M.D., Professor and Director, Department of Medicine, Seton Hall College of Medicine and Dentistry.

A. Pathological Diagnoses:

1. Chronic pancreatitis with extensive loss of acinar tissue.
2. Atrophy of mucosa, ileum and jejunum.
3. Septicemia.

REVIEWS

Glaucoma: Transactions of the Second Conference, December 3, 4, and 5, 1956, Princeton, New Jersey. Edited by FRANK W. NEWELL, M.D., Department of Surgery, University of Chicago, Chicago, Ill. 245 pages; 15.5 × 23.5 cm. Sponsored by the Josiah Macy, Jr. Foundation, New York. 1957. Price, $4.95.

In the introduction to this book mention is made of the style of publications of Transactions of the Josiah Macy, Jr. Foundation conference programs. This type of publication seems to have aroused considerable interest and criticism, the latter being levelled at a conference publication characterized by a verbatim report of interruptions, questions, remarks, by various members of the discussion group, and to some readers this criticism may not seem unjustifiable. On the other hand, occasional texts of this sort provide a welcome deviation from the usual textbook. It would seem at first that an intricate subject, such as glaucoma, would not adapt itself suitably to this type of publication. However, the overall result in the case of this book is eminent, both in the presentation of the subject matter and its quality of maintaining the reader's interest.

This is not an easy book to read, nor is it a manual of quick reference. It is a scholarly work, and this reviewer reserves the word "scholarly" only for those books that have proved to be milestones in the field of medical education. What at first reading seems to be a theoretical discussion of purely abstract concepts soon resolves itself upon reflection into a workable basis for what is hoped to be an ultimate solution to this complex problem of glaucoma.

It can be said without contradiction that no other bodily structure comparable to the size of the anterior chamber angle of the eye has stimulated or produced so much research, not only in the field of physiology, but also pharmacology, physics, chemistry, and perimetry. Study of the delicate mechanism regulating the flow of aqueous, and the disastrous results that follow imbalance of aqueous inflow and outflow, namely that of blindness, has intensified research in many countries for the past several years. As with any unsolved scientific problem, there are many contradictions and diversified theories.

This book happily avoids much that is controversial. It clarifies all that is currently accepted by most investigators and ophthalmologists. The chapters concerning mechanisms of aqueous formation, mathematical formulation of the dynamics of aqueous, and the transport mechanisms by membranes are interestingly presented and well illustrated by diagrams that are self-explanatory and simply constructed. They are a very valuable adjunct to the entire format of the book. The chapter dealing with clinical glaucoma is somewhat unique in that it stresses the mechanism by which increased intraocular tension causes loss of visual field and changes in the optic nerve, rather than burdening itself with the question of the origin of the increase in intraocular tension. All the important work in this field for the last several years is very compactly summarized, and includes all the essentials of many articles, sparing the reader much time in referring to the original articles. A fairly large section of the book toward the end concerns itself with the problem of applanation tonometry, and again this reviewer feels that such lengthy discussion is certainly in order. All the elementary principles of such tonometry are discussed and clarified with the use of many tables and diagrams.

The overall impression of this reviewer is that no words have been wasted in presenting this book, laborious discussion of side issues and controversial theories

is avoided; the book on the whole is a definite constructive contribution to the literature of ophthalmology.

JOHN C. OZAZEWSKI

The Medical Management of Cancer, Modern Medical Monographs 16. By HENRY D. DIAMOND, M.D., F.A.C.P. 179 pages; 14.5 × 22.5 cm. Grune & Stratton, New York. 1958. Price, $6.75.

This volume is part of the Modern Medical Monographs series which is edited by Drs. Irving S. Wright and Richard H. Orr.

Dr. Diamond's experience with cancer and its management has been at the Memorial Center for Cancer in New York and the Sloan-Kettering Institute for Cancer Research.

The book is divided into two sections and an appendix. The first section deals with cancers in which medical (non-surgical) therapy is the primary form of treatment. These include the lymphomas, the leukemias, and plasma cell myeloma. The second section considers the medical management of those cancers in which primary treatment is or might have been surgical, such as cancer of the lung, thyroid, ovary, breast and prostate. The appendix is devoted to a review of the use of the radioisotopes in the control of cavitary effusions.

The material is clearly and concisely presented with efficient use of illustrative photographs and tables. The book should be of great help to the generalist and internist who must be acquainted with current principles and methods of management of the cancer patient. Its lucid brevity leads one to look for more information which can be obtained through perusal of the extensive current literature documented in the bibliographies.

P. B. S.

Heart Disease in Infancy and Childhood. By JOHN D. KEITH, M.D., RICHARD D. ROWE, M.D., and PETER VLAD, M.D. 877 pages; 18 × 26 cm. The Macmillan Company, New York. 1958. Price, $22.50.

Congenital heart disease was for long the Cinderella of cardiology and like her, once famous, has caused much ink to flow. This new book from the Hospital for Sick Children, Toronto, is detailed, comprehensive and excellently produced. The authors are a brilliant and enthusiastic team and their book reflects their wide experience and original approach. The tone of the book is set by the preface which shows understanding of the rapid growth and changing concepts of the subject and an unusual graciousness in describing the contributions of others. The early chapters are devoted to embryology and special studies, the chapter on catheterization being especially useful and well written. The major part of the book is devoted to detailed analysis of the various congenital malformations. The authors have a particularly wide experience with small infants and their assessment of the danger signs in infants with pulmonary stenosis, patent ductus and other operable malformations in infants is outstanding. The chapter on coarctation is excellent in its positive approach to diagnosis and management.

The figures given for incidence and age at death in various malformations are useful and clearly illustrated in graphic form, although it is not always made clear which figures are based on Toronto experience alone and which on the literature. In general, however, the recent literature is extensively and ably used to amplify discussion and indicate both the breadth of current knowledge and the numerous

lacunae. In a few instances, notably the chapter on aortic stenosis, this wide reading and tolerant approach has led to quotation from articles based on unproved cases and possibly better left unread. There is nevertheless, no other textbook on this subject which discloses wider reading or a more intellectual analysis of the problems which still remain controversial.

The illustrations deserve comment. Most are excellent and a few, for example a diagram illustrating the varying origin of the aorta as visalized angiocardiographically, are striking and original. The angiocardiograms, particularly of the complicated malformations, are admirable. A few of the x-rays have defeated the publisher's art and it is perhaps unfortunate that the roentgenogram and electrocardiogram of fibroelastosis seem much more likely to have come from a case of myocarditis.

The last quarter of the book is devoted to rheumatic and other collagen disorders and cardiac involvement in metabolic and neurological diseases. The cardiac changes in gargoylism are particularly well reviewed, whereas the discussion of progressive muscular dystrophy ignores the early ST and T wave changes indicative of early cardiac involvement and does little to clarify the confused literature on this subject. The appendix on drugs and the illustrated table of clinical features of congenital malformations are valuable for those beginning the subject.

This is an invaluable book for the pediatrician and a stimulating and useful one for the internist whose knowledge of congenital heart disease in adults invariably needs supplementing before he can safely encounter the more urgent and complex diagnostic problems of infancy and childhood.

C. A. N.

Endocrine Aspects of Breast Cancer: Proceedings of a Conference held at the University of Glasgow, 8th to 10th July, 1957. Edited by ALASTAIR R. CURRIE, B.Sc., M.B., F.R.C.P.Ed; foreword by C. F. W. ILLINGWORTH, C.B.E., M.D., Ch.M., F.R.C.S.Ed., F.R.F.P.S. 340 pages; 14.5 × 22.5 cm. The Williams & Wilkins Co., Baltimore. 1958. Price, $8.50.

This 340 page book covers the proceedings of a conference held at the University of Glasgow, 8th to 10th July, 1957, on Endocrine Aspects of Breast Cancer. In this volume, the presentations have been printed in full together with summary discussions which followed the talks. In addition, the authors have given a clinical commentary to consolidate the discussions. Eighty participants from the British Isles, Sweden, Germany, Italy, Holland and America took part in the program.

This volume is organized into four parts: Part I includes experiences with adrenalectomy, hypophysectomy and various types of pituitary ablation. Part II on pathology includes histological and chemical studies on the adrenal and pituitary glands from patients suffering with carcinoma of the breast. In addition, this section includes microanatomy of the breast as a result of changes in the hormonal environment. Part III is composed of hormone studies which consider urinary estrogens and urinary 17-oxosteroids. The final chapter is devoted to experimental pathology and includes some interesting experiments relative to breast cancer.

This extremely valuable volume presents contributions from many outstanding men in the field discussing various aspects of this frequent and perplexing problem of breast cancer. To anyone interested in this subject, this publication is of great assistance in evaluating the newer forms of palliative therapy in the treatment of metastatic breast cancer.

H. C. H.

Auscultation of the Heart. By ABE RAVIN, M.D. 166 pages; 14.5 × 22.5 cm. The Year Book Publishers, Inc., Chicago. 1958. Price, $6.00.

With the ever increasing emphasis on the newer methods of cardiac diagnosis, it is reassuring to see a text devoted to a more routine but not sufficiently stressed technic. The author includes discussion on sound, the stethoscope, graphic recording of auscultation, heart sounds, murmurs, and specific disease entities. He suggests the routine use of a chart for the graphic recording of heart sounds and murmurs, and includes frequent examples of its application. Although one might take exception to certain specific statements such as, "very little happens to a heart that it does not give some auscultatory clue to the trained observer," the text can be recommended as a well organized, clearly written book for students and physicians alike. A detailed index adds to the value of this text.

L. S.

Textbook of Clinical Neurology, with an Introduction to the History of Neurology. 8th Ed. By ISRAEL S. WECHSLER, Consulting Neurologist, The Mount Sinai Hospital, New York. 782 pages; 16 × 24.5 cm. W. B. Saunders Co., Philadelphia. 1958. Price, $11.00.

This is the eighth edition of Dr. Wechsler's textbook. This edition preserves many of the features which have made this text so popular for so long. As is proper in a student text, he has shortened those sections dealing with the less frequent neurologic conditions and deals more extensively with the more common conditions. The section on the neurologic examination is, in this reader's opinion, one of the best sections in the book. The introduction to the history of neurology has been preserved, with an extensive bibliography, and probably remains one of the few sources on the history of neurology which is readily available for the medical student. Any criticisms of this text would be directed toward the great emphasis on signs and symptoms at the expense of other important considerations of diseases of the nervous system. There are short bibliographies following certain of the sections but none with respect to others. The index is complete and useful.

Dr. Wechsler's text remains an excellent textbook for Clinical Neurology.

C. V. B.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Electrocardiography. Edited by CHARLES E. KOSSMANN, B.S., M.D., Med. Sc.D., F.A.C.P., Associate Professor of Medicine, New York University College of Medicine, etc. 280 pages; 24 × 15.5 cm. 1958. Grune & Stratton, New York. Price, $9.75.

The Agreement of Brussels, 1924, Respecting Facilities to be Given to Merchant Seamen for the Treatment of Venereal Diseases: Report of a Study Group. World Health Organization Technical Report Series No. 150. 63 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Amélioration et Reproduction des Radiographies par Modulation Électronique le Logetron. Radio-Diagnostic et Radio-Anatomie de Précision. Par A. JUTRAS et H. FISCHGOLD. 122 pages; 27 × 22 cm. (paper-bound). 1958. Masson & Cie, Paris. Price, 4.500 fr.

Atlas de Radiologie Clinique de "La Presse Médicale," *Serie 1 à 100 (1953–1958).* 400 pages; 35 × 26.5 cm. (boxed). 1958. Masson & Cie, Paris. Price, 4.000 fr.

Biophysical Principles of Electrocardiography. Volume I of *Electrocardiographic Analysis.* By ROBERT H. BAYLEY, M.D., Professor of Internal Medicine, Director of Heart Station, University of Oklahoma School of Medicine and University Hospitals, Oklahoma City. 237 pages; 26 × 17.5 cm. 1958. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $8.00.

Le Cancer de la Corde Vocale. Monographies Oto-rhino-laryngologiques Internationales. Fondées par M. VERNET. Publiées par G. PORTMANN, M. SOURDILLE, J. TERRACOL et M. VERNET. Par J. PIQUET. 204 pages; 25 × 16.5 cm. (paper-bound). 1958. Masson & Cie, Paris. Price, 1.600 fr.

Cardiovascular Diseases. 3d Ed. By DAVID SCHERF, M.D., F.A.C.P., Professor of Clinical Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, and LINN J. BOYD, M.D., F.A.C.P., Professor and Director of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals. 829 pages; 25 × 17.5 cm. 1958. Grune & Stratton, New York. Price, $17.75.

Cardiovascular Diseases in the U. S.—Facts and Figures. 15 pages; 21.5 × 28 cm. (paper-bound). 1958. American Heart Association in cooperation with the National Heart Institute and Heart Disease Control Program, New York. Single copies of the booklet may be obtained without cost by writing the National Heart Institute, Public Health Service, Bethesda 14, Maryland, or the American Heart Association, 44 East 23rd Street, New York 10, New York. Additional copies may be purchased from the American Heart Association at 15¢ per copy, $15 per 100 copies.

The Cerebrospinal Fluid: Production, Circulation and Absorption. Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and CECILIA M. O'CONNOR, B.Sc. 335 pages; 21 × 14 cm. 1958. Little, Brown and Company, Boston. Price, $9.00.

Classification of Atherosclerotic Lesions: Report of a Study Group. World Health Organization Technical Report Series No. 143. 20 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Clinical Heart Disease. 5th Ed. By SAMUEL A. LEVINE, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School, etc. 673 pages; 25.5 × 16.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $9.50.

Current Therapy, 1958: Latest Approved Methods of Treatment for the Practicing Physician. Edited by HOWARD F. CONN, M.D.; Consulting Editors: GEORGE E. BURCH, M. EDWARD DAVIS, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, CLARENCE S. LIVINGOOD, PERRIN H. LONG, H. HOUSTON MERRITT, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS and ROBERT H. WILLIAMS. 827 pages; 27 × 20.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $12.00.

Diagnostic Laboratory Hematology. 2nd Ed. By GEORGE E. CARTWRIGHT, M.D., Professor of Medicine, College of Medicine, University of Utah, Salt Lake City, Utah. 250 pages; 22.5 × 14.5 cm. 1958. Grune & Stratton, Inc., New York. Price, $6.75.

Discovering Ourselves: A View of the Human Mind and How it Works. 3d Ed. By EDWARD A. STRECKER, M.D., Sc.D., and KENNETH E. APPEL, M.D., Sc.D., in collaboration with JOHN W. APPEL, M.D., The Department of Psychiatry, University of Pennsylvania. 303 pages; 21.5 × 14.5 cm. 1958. The Macmillan Company, New York. Price, $4.75.

Drugs of Choice, 1958–1959. WALTER MODELL, M.D., Editor, Associate Professor of Pharmacology, Cornell University Medical College, etc. 931 pages; 25.5 × 17.5 cm. 1958. The C. V. Mosby Company, St. Louis. Price, $12.75.

The Essence of Surgery. By C. STUART WELCH, M.S., M.D., Ph.D., Professor of Surgery, Albany Medical College of Union University; and SAMUEL R. POWERS, JR., A.B., M.D., M.Sc.D., Professor of Experimental Surgery, Albany Medical College of Union University. 320 pages; 24 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $7.00.

Essentials of Gynecology. By E. STEWART TAYLOR, M.D., Professor and Head of the Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, Colorado. 502 pages; 24 × 16 cm. 1958. Lea & Febiger, Philadelphia. Price, $12.00.

Expert Committee on Biological Standardization: Eleventh Report. World Health Organization Technical Report Series No. 147. 38 pages; 24 × 16 cm. (paperbound). 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Fundamentals of Neurology. 3d Ed. By ERNEST GARDNER, M.D., Professor of Anatomy, Wayne State University College of Medicine, Detroit. 388 pages; 22.5 × 14.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $5.75.

Geschlecht und Krankheit. By PROFESSOR DR. med. MAX BÜRGER. 516 pages; 23 × 16.5 cm. 1958. J. F. Lehmanns Verlag, Munich. Price, DM 60.00 cloth.

Gestation: Transactions of the Fourth Conference, March 5, 6 and 7, 1957, Princeton, N. J. Edited by CLAUDE A. VILLEE, Ph.D., Associate Professor of Biological Chemistry, Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts. 216 pages; 24 × 15.5 cm. 1958. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.50.

Gynecologic and Obstetric Pathology, With Clinical and Endocrine Relations. 4th Ed. By EMIL NOVAK, A.B., M.D., D.Sc. (Hon., Trinity College, Dublin; Tulane), F.A.C.S., F.R.C.O.G. (Hon.), Late Assistant Professor Emeritus of Gynecology, The Johns Hopkins Medical School, etc.; and EDMUND R. NOVAK, A.B., M.D., Assistant Professor of Gynecology, The Johns Hopkins Medical School, etc. 650 pages; 25.5 × 16.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $14.00.

Manual of Medical Emergencies. 3d Ed. By STUART C. CULLEN, M.D., Professor of Surgery; Chairman, Division of Anesthesiology, State University of Iowa College of Medicine; and E. G. GROSS, M.D., Professor and Head of Department of Pharmacology, State University of Iowa College of Medicine. 302 pages; 18 × 12.5 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $5.75.

Modern Clinical Psychiatry. 5th Ed. By ARTHUR P. NOYES, M.D., Superintendent, Norristown State Hospital, Norristown, Pennsylvania; and LAWRENCE C. KOLB, M.D., Professor and Executive Officer, Department of Psychiatry, College of Physicians and Surgeons, Columbia University, etc. 694 pages; 24 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $8.00.

Neuropathology. By J. G. GREENFIELD, M.D., F.R.C.P., LL.D., Consulting Pathologist, National Hospital for Nervous Diseases, London; W. BLACKWOOD, M.B., Ch.B., F.R.C.S.E., M.R.C.P.E., Pathologist, National Hospital for Nervous Diseases, London; W. H. MCMENEMEY, M.A., D.M., F.R.C.P., Pathologist, Maida Vale Hospital for Nervous Diseases, London; A. MEYER, M.D., Emeritus Professor of Neuropathology (Institute of Psychiatry), University of London; and R. M. NORMAN, M.D., M.R.C.P., D.P.M., Neuropathologist, Burden Mental Research Department, Frenchay Hospital, Bristol. 640 pages; 25.5 × 19 cm. 1958. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, $20.00.

Orr's Operations of General Surgery. 3d Ed. By GEORGE A. HIGGINS, M.D., F.A.C.S., Associate Professor of Surgery, University of Kansas School of Medicine, etc.; and THOMAS G. ORR, JR., M.D., F.A.C.S., Associate in Surgery, University of Kansas School of Medicine, etc. 1,016 pages; 26 × 18.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $20.00.

Orthopedic Diseases: Physiology—Pathology—Radiology. By ERNEST AEGERTER, M.D., Professor of Pathology and Director of the Department of Pathology, Temple University Medical Center and School of Medicine, etc.; and JOHN A. KIRKPATRICK, JR., M.D., Radiologist, St. Christopher's Hospital for Children, etc. 602 pages; 25.5 × 16.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $12.50.

The Pasteur Fermentation Centennial, 1857–1957: A Scientific Symposium on the Occasion of the One Hundredth Anniversary of the Publication of Louis Pasteur's Mémoire sur la fermentation appelée lactique. 207 pages; 23.5 × 15.5 cm. 1958. Chas. Pfizer & Co., Inc., New York.

Pathology for the Physician. 6th Ed. By WILLIAM BOYD, M.D., Dipl. Psychiat., M.R.C.P. (Edin.), Hon. F.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (Can.), F.R.S. (Can.), LL.D. (Sask.), (Queen's), D.Sc. (Man.), M.D. (Oslo), Professor Emeritus of Pathology, The University of Toronto, etc. 900 pages; 26.5 × 18.5 cm. 1958. Lea & Febiger, Philadelphia. Price, $17.50.

A Practical Manual on the Medical and Dental Use of X-Rays with Control of Radiation Hazards. Prepared by THE AMERICAN COLLEGE OF RADIOLOGY for Users of X-Rays in the Healing Arts. Text by RICHARD H. CHAMBERLAIN, M.D., with the assistance of ROBERT J. NELSEN, D.D.S. and the Commission on Units, Standards, and Protection of The American College of Radiology. 31 pages; 22 × 15.5 cm. (paper-bound). 1958. The American College of Radiology, Chicago. Distributed without charge, but for subsequent individual or bulk requests, 25¢.

Praktikum der Immunohämatologie. Von PROF. DR. med. H. H. HENNEMANN; unter Mitarbeit von L. RANKE. 166 pages; 21 × 15 cm. (leather-bound). 1958. VEB Georg Thieme, Leipzig. Price, geb. 20.–

The Preservation of Youth: Essays on Health. By MOSES BEN MAIMON (MAIMONIDES); translated from the original Arabic (Fi Tadbir as-Sihha) and with an introduction by HIRSCH L. GORDON, M.D., Ph.D., D.H.L. 92 pages; 19 × 12 cm. 1958. Philosophical Library, New York. Price, $2.75.

A Primer on Common Functional Disorders: Practical Diagnosis and Management. By JACK W. FLEMING, M.D., Department of Internal Medicine, The Medical Center Clinic, Pensacola, Florida; with illustrations by JERRY ROBINSON. 174 pages; 21 × 14 cm. 1958. Little, Brown and Company, Boston. Price, $5.00.

Procedures for the Testing of Intentional Food Additives to Establish Their Safety for Use: Second Report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization Technical Report Series No. 144. 19 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Progress in Arthritis. Edited by JOHN H. TALBOTT, M.D., and L. MAXWELL LOCKIE, M.D. 456 pages; 24 × 15.5 cm. 1958. Grune & Stratton, New York. Price, $12.50.

Psychoendocrinology. Edited by MAX REISS, M.D., D.Sc., Neuroendocrine Research Unit, Willowbrook State School, Staten Island, New York; with 23 contributors. 208 pages; 22.5 × 14.5 cm. 1958. Grune & Stratton, New York. Price, $7.00.

Reflexogenic Areas of the Cardiovascular System. By C. HEYMANS, M.D., Professor of Pharmacology, University of Ghent; and E. NEIL, M.D., D.Sc., John Astor Professor of Physiology, University of London, etc. 271 pages; 25.5 × 19 cm. 1958. Little, Brown and Company, Boston. Price, $10.00.

Les Sinusites de l'Enfance. Monographies Oto-rhino-laryngologiques Internationales. Fondées par M. VERNET. Publiées par G. PORTMANN, M. SOURDILLE, J. TERRACOL et M. VERNET. Par J. TERRACOL et Y. GUERRIER. 166 pages; 25 × 16.5 cm. (paper-bound). 1958. Masson & Cie, Paris. Price, 1.400 fr.

A Text on Systemic Pathology. Vol. I. Edited by OTTO SAPHIR, M.D., Director, Department of Pathology, Michael Reese Hospital, Chicago, Illinois, etc.; with special contributors. 865 pages; 28 × 20.5 cm. 1958. Grune & Stratton, New York. Price, $32.00.

A Textbook of Clinical Neurology, With an Introduction to the History of Neurology. 8th Ed. By ISRAEL S. WECHSLER, M.D., Consulting Neurologist, The Mount Sinai Hospital, New York. 782 pages; 24.5 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $11.00.

A Textbook of Psychology. By DONALD OLDING HEBB, Professor and Chairman, Department of Psychology, McGill University. 276 pages; 24.5 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $4.50.